Bedaquiline tablets 100 mg
SIRTURO™

DOSAGE FORMS AND STRENGTHS

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 section *List of Excipients.*

CLINICAL INFORMATION

Indication

SIRTURO™ is indicated in adults (≥ 18 years) as a part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug resistant *Mycobacterium tuberculosis.*

Dosage and Administration

SIRTURO™ should only be administered as part of a multidrug 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 national TB treatment guidelines for direction on selection and duration of use of companion drugs. 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.
Throughout treatment with, and following the last intake of SIRTURO™, patients should continue to take their companion drugs in accordance with national TB treatment guidelines and local MDR-TB treatment practice.

Dosage – Adult (≥ 18 years)

The recommended dosage of SIRTURO™for MDR-TB is:

- Weeks 1-2: 400 mg (4 tablets of 100 mg) **once daily**
- Weeks 3-24: 200 mg (2 tablets of 100 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.

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 600 mg (taken as 3 intakes of 200 mg per day, at least 24 hours apart).

Special populations

Pediatrics (<18 years of age)

The safety and efficacy of SIRTURO™ in children and adolescents less than 18 years of age 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 *Pharmacokinetics*). It is recommended that the SIRTURO™ tablet be swallowed whole with water.

Contraindications

None known

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). Therefore, use of SIRTURO™ in these settings is not recommended.

Mortality

In the 120-week C208 trial 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, 10 patients died in the SIRTURO™ treatment group (N = 79) compared to 2 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 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.

Cardiovascular safety

During clinical trials 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.

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

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 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), 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 were seen in clinical trials 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 bedaquiline and rifamycins (rifampin, rifapentine and rifabutin) or other potent CYP3A4 inducers used systemically should therefore be avoided.

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 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 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 bedaquiline and rifamycins (rifampin, rifapentine and rifabutin) or other potent CYP3A4 inducers used systemically should be avoided.

The short-term co-administration of bedaquiline and ketoconazole in healthy 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 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 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

In an interaction study of single-dose bedaquiline and multiple-dose lopinavir/ritonavir, exposure (AUC) to bedaquiline was increased by 22% [90% CI (11; 34)]. Co-administration of single-dose bedaquiline and multiple-dose nevirapine did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on the combined use of these antiretroviral agents 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, 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, 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).

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*).

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™.

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.

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 1. 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 1: All Adverse Drug Reactions from Controlled Trials 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)
Diarrhoea	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 from the uncontrolled study C209 (N=233) nor from the Phase 1 and 2 studies.

Deaths:

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 2 for a summary of deaths in the C208 trial.

Table 2: Summary of Deaths During the C208 Trial

[TRADE NAME]/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

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 [TRADE NAME] was administered

Cardiovascular safety:

In the controlled Phase 2b study (C208), 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 223 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*).

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 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. Removal of unabsorbed bedaquiline may be achieved by gastric lavage or aided by the administration of activated charcoal. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma. Clinical monitoring should be considered.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: To be confirmed, 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).

Mechanisms of resistance

Mycobacterial resistance mechanisms that affect bedaquiline include modification of the *atpE* target gene. Not all isolates with increased MICs have *atpE* mutations, suggesting the existence of at least one other mechanism of resistance. Isolates with decreased susceptibility to bedaquiline tend to be less susceptible to clofazimine.

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 Technique

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 resazurin microtiter assay (REMA) 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 3.

Method for Bedaquiline Minimal Inhibitory Concentration Determination in 7H11 Agar Medium

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

M. tuberculosis isolates are grown on 7H11 agar medium (or Lowenstein-Jensen medium). Colonies are subcultured in 7H9 broth supplemented with 10% oleic acid, albumin, dextrose, and catalase 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 ~10^8 CFU/mL of microorganisms.

0.1 mL of dilutions of 10^0, 10^{-1} and 10^{-2} of the MTB suspension is inoculated in all drug- containing 7H11 agar medium. For the control 0.1 mL of dilutions 10^0, 10^{-1}, 10^{-2} and 10^{-3} of MTB suspension is inoculated in drug-free agar medium. The tubes are incubated in an inclined position overnight at room temperature making sure that the solution covers the surface of the tubes. The next day, the tubes are

incubated standing at 37°C and 5% CO_2 for at least one week with the caps loose. In case 7H11 agar plates are used, the plates are incubated with the lid in the upright position overnight. The next day, the plates are turned (the lid is then in the lower position) and incubated until reading.

Report results at 21 days post-inoculation. In case the control slopes or plates show insufficient growth at 21 days, these will be read weekly until a maximum of 42 days post-inoculation. If there is still insufficient growth at 42 days, the strain is re-inoculated for repeat testing one more time. The percentage of resistant bacilli in each concentration of drug is calculated.

The following formula is used to determine the MIC defined as the lower drug concentration that inhibits 99% of the growth:

$$\text{RATIO COLONIES} = \frac{\text{Colony count on drug medium at } 10^{0}}{\text{Colony count on control medium at } 10^{-2}} = \text{MIC (if} \leq 1)$$

- If the RATIO COLONIES is ≤ 1, this concentration is the MIC.
- If the RATIO COLONIES is > 1, this concentration is not the MIC and the following concentration has to be read.

Note: Polystyrene tubes or plates should be used with 7H11 agar for testing of bedaquiline. Lowenstein-Jensen medium should not be used.

Method for Bedaquiline Minimal Inhibitory Concentration Determination Using Resazurin Microtiter Assay (REMA) in 7H9 Broth Medium

A 200 µg/mL working solution is made in DMSO and used to prepare 2-fold serial dilutions in DMSO (from 200 µg/mL to 0.8 µg/mL). 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. These 100X working solutions are then diluted 1/100 in 7H9 medium to obtain the final Clinical and Laboratory Standards Institute (CLSI) concentrations of 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015 and 0.008 µg/mL.

M. tuberculosis isolates are grown on 7H11 medium (or Lowenstein-Jensen). Colonies are subcultured in Middlebrook 7H9 broth supplemented with 10% (oleic acid, albumin, dextrose, and catalase), 0.5% glycerol and 0.1% casitone (7H9-S) 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 ~10^{8} CFU/mL of microorganisms. A 100 µl of 7H9-S broth is added to all

microtiter wells. A 100 µl of the working solutions of bedaquiline is added to wells except the growth control wells.

Using tips with filters inoculate the plates with 100 µl of the inoculum (dilution 1:10) to all wells including the growth control well but not in the well containing the negative control. After inoculation, the plates are sealed in plastic bags and incubate at 37°C for 7 days.

A 0.01% or 0.02% resazurin solution is prepared in distilled water, sterilized by filtration through a 0.2 µm, kept at 4°C for 1-2 weeks and protected from light.

After 7 days incubation, the plates are taken from the incubator and 30 µl of resazurin at 0.01 % or 0.02% is added to all the wells. The plates are then sealed again and incubated overnight for color development.

A change in color from blue to pink means a growth of the isolate at that concentration of the drug. The minimal inhibitory concentration (MIC) of bedaquiline is interpreted as the lowest concentration that prevents a change in color of the resazurin.

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.
Polystyrene plates should be used with REMA for testing of bedaquiline.

Table 3. Susceptibility Test Result Interpretive Criteria for Bedaquiline

Pathogen	Minimum Inhibitory Concentration (µg/mL)	
	7H1 Agar	REMA (7H9broth)
	Susceptible Only (S)	Susceptible Only (S)
M. tuberculosis	≤0.5	≤0.25

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 (for REMA) 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 4.

Table 4. Acceptable Quality Control Ranges for Bendaquiline

QC Organism	Recommended Bedaquiline MIC (µg/mL)	
	7H11 Agar	REMA (7H9broth)
	Susceptible Only (S)	Susceptible Only (S)
M. tuberculosis H37Rv	0.03 – 0.12	0.03 – 0.12

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 µg/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.

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.

Clinical studies

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 (BR) of MDR-TB medication consisting of ethionamide (ETH), kanamycin (KAN), pyrazinamide (PZA), ofloxacin (OFL), and cycloserine/terizidone. 63.1% of the 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.

Trial C208 is ongoing. Although the 24 week SIRTURO™ treatment period has been completed by all patients the BR treatment period and the subsequent treatment free follow up period have not been completed by all patients.

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 BR 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 intention to treat (mITT) population with sputum culture conversion after 24 weeks of treatment with SIRTURO™ or placebo in combination with BR (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 results of the all available data (beyond 72 weeks and up to efficacy interim analysis cut-off date). The proportion of responders (with patients who discontinued considered as non responders) was 44/66 (66.7%) in the SIRTURO™ group and 31/66 (47.0%) in the placebo group.

Table 5: Culture conversion Status

Culture Conversion Status[a], n (%)	mITT population	
	SIRTURO™/BR N = 66	Placebo/BR N = 66
Overall responder[b]	44 (66.7)	31 (47.0)
Overall non-responder	22 (33.3)	35 (53.0)
Failure to convert	*8 (12.1)*	*15 (22.7)*
Relapse[c]	*5 (7.6)*	*8 (12.1)*
Discontinued but converted	*9 (13.6)*	*12 (18.2)*

mITT = modified intent-to-treat

[a] Beyond Week 72 and up to the efficacy interim analysis cut-off date

[b] Patients who discontinued considered as non-responders

[c] Relapse is defined 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. Sixty-four percent of the 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, 173 patients had isolates with full characterization of resistance status. 53.8% (93/173) of patients were infected with an MDR strain, 25.4% (44/173) of patients were infected with a pre-XDR strain, and 20.8% (36/173) 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 OFL: (52.4%) and levofloxacin: (30.5%)], PZA (76.0%), aminoglycosides (71.7%; mainly KAN: 49.8%), and ethambutol (51.5%). Other baseline BR 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 BR in accordance with national TB program (NTP) treatment guidelines. The 24 week SIRTURO™ treatment period has been completed by all patients.

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 (55.6%; 20/36) in XDR-TB patients. Responder rates were higher for patients on 3 or more potentially active drugs *in vitro* in their BR.

Although there were differences in BR regimens used across trials, safety results were generally similar between trials C208 and C209.

Trial C209 is ongoing; the BR-only treatment period and the subsequent treatment-free follow up period of at least 24 weeks (6 months) have not been completed by all patients.

Clinical Study Evaluating the QTc interval

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 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 (see *Warnings and Precautions*).

Pharmacokinetic Properties

Absorption

After oral administration bedaquiline is well absorbed. Maximum plasma concentrations (Cmax) are typically achieved at about 5 hours post dose. Cmax 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).

Elimination

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 Cmax, 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 (< 18 years of age)

The pharmacokinetics of SIRTURO™ in pediatric patients have not been evaluated.

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 (AUC672h) 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*).

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.

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.

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.

PHARMACEUTICAL INFORMATION

List of Excipients

- 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)

Incompatibilities

Not applicable.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Keep out of the sight and reach of children.

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

Nature and Contents of Container

188 tablets packaged in a white high density polyethylene (HDPE) bottle with child-resistant polypropylene (PP) closure with induction seal liner.

Instructions for Use and Handling <and Disposal>

Not applicable.

Manufactured By

Janssen Pharmaceutica N.V.,
Turnhoutseweg 30, B-2340,
Beerse, Belgium

Imported by:

Johnson & Johnson Limited
Gala No. 1 to 10, Bldg. No. J-2, Ground Floor,
Shree Arihant Complex, Kalher,
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Marketed in India by:

Johnson & Johnson Ltd, L.B.S. Marg, Mulund (West), Mumbai 400080

Reference: Company Core Data Sheet (CCDS) dated 24 Mar 2014.