SIRTURO®

Bedaquiline

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SIRTURO 100 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bedaquiline fumarate equivalent to 100 mg of bedaquiline.

Excipients with known effect:

Each tablet contains 145 mg of lactose (as monohydrate).

For the full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Tablet.

SIRTURO is supplied as an uncoated, white to almost white round biconvex tablet with debossing of "T" over "207" on one side and "100" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of 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.

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)

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, as administration with food increases bioavailability (see **section 5.2 Pharmacokinetic Properties - Absorption**). It is recommended that the SIRTURO tablet be swallowed whole with water.

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

Paediatrics (18 years of age and younger)

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 and older)

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 haemodialysis or peritoneal dialysis, SIRTURO should be used with caution (see **section 5.2 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 **section 5.2 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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 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 **section 4.8 Undesirable effects**). After enrolment, 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 **section 4.8 Undesirable effects**.

Cardiovascular safety

During clinical trials with SIRTURO a prolongation of QTc interval was observed (see **section 4.8 Undesirable effects**). 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 **section 4.5 Interactions with other medicines and other forms of 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 **section 4.5 Interactions with other medicine and other forms of 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 during administration of SIRTURO with the background regimen (see **section 4.8 Undesirable effects**). 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.

4.5 Interactions with other medicines and other forms of interaction

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 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.

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.

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 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.

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.

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.

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.

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

Lopinavir/ritonavir

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)]. Clinical data on the combined use of lopinavir/ritonavir and SIRTURO in HIV/MDR-TB co-infected patients are not available (see **section 4.4 Special warning and precautions for use**). 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 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 **section 4.4 Special warnings and precautions for use**).

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 **section 4.4 Special warnings and precautions for use**).

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 **section 4.4 Special warnings and precautions for use**).

4.6 Fertility, pregnancy and lactation

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. 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.

Breastfeeding

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.

Because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from SIRTURO therapy taking into account the benefit of breastfeeding 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.

4.7 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.

4.8 Undesirable effects

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.

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)
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 from the uncontrolled study C209 (N = 233) nor from the Phase 1 and 2a studies

Deaths

In the C208 trial, there were more deaths reported in the SIRTURO treatment group (see **section 4.4 Special warnings and precautions for use**). 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

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

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 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 **section 4.4 Special warnings and precautions for use**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 subjects receiving a single 800 mg dose of SIRTURO, adverse reactions were consistent with those observed in clinical studies at the recommended dose (see **section 4.8 Undesirable effects**).

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. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma. Clinical monitoring should be considered.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, other 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 (IC50 > 100 µM), resulting in a selectivity index of > 10000 compared to the mycobacterial ATP synthase (IC50 0.01 µM).

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.

Lists of microorganisms

Bedaquiline has been shown to be active against most isolates of *Mycobacterium tuberculosis*, both *in vitro* and in clinical infections (see **section 4.1 Therapeutic 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.

For specific information regarding susceptibility test interpretive criteria please refer to Table 3. The quality control standard for the broth microdilution MIC is 0.015 – 0.12 micrograms/mL.

Table 3. Susceptibility Test Result Interpretive Criteria for Bedaquiline

Testing Method	CC (mcg/mL)	Susceptible	Resistant
7H9 Broth MIC[a,c]	NA	≤0.12	≥0.25
MGIT 960[c,d]	1	GU ≤100	GU >100
AP[b,c,d]	0.25	<1%	≥1%

AP: agar proportion, CC: critical concentration; GU: growth unit; mcg: microgram, MGIT: mycobacteria growth indicator tube, MIC: minimum inhibitory concentration, NA: not applicable.

[a] MIC breakpoint (mcg/mL). Applies to both frozen and dry microtiter plates.

[b] Applies to both 7H10 and 7H11 agar media.

[c] CLSI. Susceptibility testing of Mycobacteria, Nocardia, and other aerobic Actinomycetes; Approved Standards-Third Edition. CLSI Document M24-A2. Wayne, PA: Clinical and Laboratory Standards Institute.

[d] World Health Organization. Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. 2018.

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.

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 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 **section 4.4 Special warnings and precautions for use**).

Clinical efficacy and safety

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 4: 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 **section 5.1 Pharmacodynamic Properties – Mechanisms of resistance**.

5.2 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).

Elimination

Based on preclinical studies, bedaquiline is mainly eliminated in faeces. 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.

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.

Special populations

Paediatrics (18 years of age and younger)

The pharmacokinetics of SIRTURO in paediatric patients have not been evaluated.

Elderly (65 years of age and older)

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 haemodialysis 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 haemodialysis 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 **section 4.2 Dose and method of 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 **section 4.4 Special warnings and precautions for use**).

5.3 Preclinical safety data

Carcinogenicity

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.

Genotoxicity

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

Fertility

See **section 4.6 Fertility, pregnancy and lactation**.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Corn starch

Croscarmellose sodium

Hypromellose 2910

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Polysorbate 20

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

SIRTURO has a shelf-life of 3 years.

6.4 Special precautions for storage

Stored at or below 30°C. Store in the original container in order to protect from light.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland

NEW ZEALAND

Telephone: 0800 800 806

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9. DATE OF FIRST APPROVAL

18 August 2016

10. DATE OF REVISION OF THE TEXT

25 May 2020

Summary table of changes

Section	Summary of new information
5.1	Updated and summarised details of dilution MIC methods