BEDAQUILINE

SIRTURO®
100 mg Tablet
Antituberculosis

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.

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

CLINICAL INFORMATION

Indications

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

Bedaquiline fumarate (Sirturo®) is indicated in adult (≥ 18 years) and pediatric patients (12 years to less than 18 years of age and weighing at least 30 kg) as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug resistant *Mycobacterium tuberculosis*.

Dosage and Administration

Bedaquiline (Sirturo®) should only be administered as part of a multi-drug resistant tuberculosis (MDR-TB) regimen. It is recommended that Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®). Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible. Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) for their specific dosing recommendations.

Dosage – Adult and Pediatric patients (12 years to less than 18 years of age)

The recommended dosage of Bedaquiline fumarate (Sirturo®) in adult and pediatric patients (12 years to less than 18 years of age) is shown in Table 1.

Table 1: Recommended dosage of Bedaquiline fumarate (Sirturo®)	
Population	**Dosing Recommendation**

Adults (18 years and older) Pediatric patients (12 years to less than 18 years of age and weighing at least 30 kg)	• **Weeks 1 to 2:** 400 mg **once daily** • **Weeks 3 to 24:** 200 mg **three times per week** (with at least 48 hours between doses).

The total duration of treatment with Bedaquiline fumarate (Sirturo®) is 24 weeks. Bedaquiline fumarate (Sirturo®) should be taken with food.

Missed dose(s)
Patients should be advised of the need to take Bedaquiline fumarate (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 Bedaquiline fumarate (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
Pediatric Patients (less than 12 years of age)
The safety and efficacy of Bedaquiline fumarate (Sirturo®) in children less than 12 years of age or weighing less than 30 kg have not been established.

Elderly (≥ 65 years of age)
There are limited clinical data on the use of Bedaquiline fumarate (Sirturo®) in elderly patients.

Renal impairment
Bedaquiline fumarate (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, Bedaquiline fumarate (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 Bedaquiline fumarate (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
Bedaquiline fumarate (Sirturo®) should be taken orally with food, as administration with food increases oral bioavailability (see ***Pharmacokinetic Properties - Absorption***). It is recommended that the Bedaquiline fumarate (Sirturo®) tablet be swallowed whole with water.

Contraindications
None known.

Warnings and Precautions
The safety and efficacy of Bedaquiline fumarate (Sirturo®) for the treatment of latent infection due to *Mycobacterium tuberculosis* has not been established. The safety and efficacy of Bedaquiline fumarate (Sirturo®) for the treatment of drug-sensitive TB has not been established. In addition, there are no clinical data on the treatment with Bedaquiline fumarate (Sirturo®) of extra-pulmonary TB (e.g. central nervous system). The safety and efficacy of Bedaquiline fumarate (Sirturo®) for the treatment of infections caused by non-tuberculous mycobacteria (NTM) have not been established. Therefore, use of Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) was administered for 24 weeks in combination with a background regimen, more deaths occurred in the Bedaquiline fumarate (Sirturo®) treatment group than in the placebo group (see ***Adverse Reactions***). After enrollment, 12.7% (10/79) patients died in the Bedaquiline fumarate (Sirturo®) treatment group (N = 79) compared to 3.7% (3/81) patients in the placebo group (N = 81). One death occurred during administration of Bedaquiline fumarate (Sirturo®). The median time to death for the remaining nine patients was 344 days after last intake of Bedaquiline fumarate (Sirturo®). One of the ten deaths in the Bedaquiline fumarate (Sirturo®) treatment group and one of the 3 deaths in the placebo group occurred after the Week 120 window. In the Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) a prolongation of QTc interval was observed (see ***Adverse Reactions***). An ECG should be obtained prior to and after initiation of therapy with Bedaquiline (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.

Bedaquiline fumarate (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.

Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline (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 Bedaquiline fumarate (Sirturo®) and/or any hepatotoxic background drug should be discontinued.

Other hepatotoxic drugs and alcohol should be avoided while on Bedaquiline fumarate (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 Bedaquiline (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 Bedaquiline (Sirturo®) in HIV/MDR-TB co-infected patients and only limited clinical data on the use of Bedaquiline (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®). In a placebo-controlled clinical study in adult patients with MDR-TB, no major impact of co-administration of Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) in HIV/MDR-TB co-infected patients are not available (see ***Warnings and Precautions***). If the benefit outweighs the risk, Bedaquiline fumarate (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 Bedaquiline fumarate (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***).

Pregnancy, Breast-feeding and Fertility
Pregnancy
There are no adequate and well-controlled studies with Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) during pregnancy unless the benefit of therapy is considered to outweigh the risks.

Breast-feeding
Bedaquiline is excreted in human milk. Limited published literature reports higher bedaquiline concentrations in human milk than in maternal plasma. In one breastfed infant, a single random plasma bedaquiline concentration was similar to maternal plasma concentration. The clinical consequence of this exposure is unknown.

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***).

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Bedaquiline fumarate (Sirturo®) and any potential adverse effects on the breastfed

infant from Bedaquiline fumarate (Sirturo®) or from the underlying maternal condition. Breastfed infants should be monitored for adverse reactions.

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 Bedaquiline fumarate (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. Refer to the prescribing information of the drugs used in combination with Bedaquiline (Sirturo®) for their respective adverse reactions.

Adverse reactions from clinical trials in adult patients

Adverse drug reactions (ADRs) for Bedaquiline fumarate (Sirturo®) were identified from pooled Phase 2b clinical trial data (both controlled and uncontrolled) containing 335 patients who received Bedaquiline fumarate (Sirturo®) in combination with a background regimen of TB drugs. The basis of assessment of causality between the ADRs and Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) in the controlled trials were nausea, arthralgia, headache, vomiting and dizziness.

Adverse drug reactions to Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®)

Adverse Drug Reactions	**Frequency**	**Bedaquiline (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 Bedaquiline fumarate (Sirturo®) treatment group (see ***Warnings and Precautions***). In the Bedaquiline fumarate (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 Bedaquiline fumarate (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

Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) was administered

In the open-label C209 trial in adult patients, 6.9% (16/233) patients died. The most common cause of death as reported by the investigator was TB (9 patients). All but one patients 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 Bedaquiline fumarate (Sirturo®) and 3.5 ms for placebo). The largest mean increase in QTcF during the 24 weeks of Bedaquiline fumarate (Sirturo®) treatment was 15.7 ms (at Week 18). After the end of Bedaquiline fumarate (Sirturo®) treatment (i.e. after Week 24), QTcF increases in the Bedaquiline fumarate (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 a clinical trial in pediatric patients (12 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 Phase 2 trial (C211) in 15 adolescent patients. The trial was designed to enroll patients from 12 years to less than 18 years of age (patients 14 years to less than 18 years of age were enrolled) with confirmed or probable (MDR-TB) infection who received Bedaquiline fumarate (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 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 Bedaquiline fumarate (Sirturo®). Observed laboratory abnormalities were comparable to those in adults. No new adverse drug reactions were identified compared to those seen in adults.

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 Bedaquiline fumarate (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 Bedaquiline fumarate (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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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).

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.

For specific information regarding susceptibility test interpretative criteria please refer to Table 4. The quality control standard for the broth microdilution MIC is 0.015-0.12 micrograms/mL.

Table 4. 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.

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 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 Bedaquiline fumarate (Sirturo®) was demonstrated in the Phase 2 studies (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 Bedaquiline fumarate (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 Bedaquiline fumarate (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.

Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) or placebo.

The addition of Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) or placebo in combination with background regimen (with patients who discontinued considered as non responders), was 52/66 (78.8%) in the Bedaquiline fumarate (Sirturo®) group and 38/66 (57.6%) in the placebo group. In the Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) group [73.3% (11/15)] vs. the placebo group [33.3% (4/12)].

Durability of response seen in the Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®) group and 29/66 (43.9%) in the placebo group.

Table 5: Culture Conversion Status

Culture Conversion Status, n (%)	mITT population	
	Bedaquiline (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 Bedaquiline fumarate (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 Bedaquiline fumarate (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%). Bedaquiline (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 Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline (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 Bedaquiline fumarate (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 (12 years to less than 18 years of age)
The pharmacokinetics, safety and tolerability of Bedaquiline fumarate (Sirturo®) in combination with a background regimen were evaluated in trial C211, a single-arm, open-label Phase 2 trial that was designed to enrol 15 adolescent patients 12 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. Bedaquiline fumarate (Sirturo®) was administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks.

The 15 patients had a median age of 16 years (range: 14-17 years), with a body weight range of 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 75.0% (6/8 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

Pediatric patients (less than 18 years of age)

The pharmacokinetics of bedaquiline and its major matabolite *N*-monodesmethyl bedaquiline (M2) in 15 adolescent patients 14 years to less than 18 years of age with MDR-TB receiving bedaquiline fumarate (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.

Individual model-based predictions showed that the population pharmacokinetics data profile from adolescent patients was similar to the population pharmacokinetics data profile obtained from adults.

The pharmacokinetics of Bedaquiline fumarate (Sirturo®) in pediatric patients less than 12 years of age or weighing less than 30 kg have not been evaluated.

Elderly (≥ 65 years of age)

There is limited clinical data on the use of Bedaquiline fumarate (Sirturo®) in TB patients aged 65 years and older.

In a population pharmacokinetic analysis of TB patients treated with Bedaquiline fumarate (Sirturo®), age was not found to influence the pharmacokinetics of bedaquiline.

Renal impairment

Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (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 Bedaquiline fumarate (Sirturo®), no clinically relevant difference in exposure between men and women were observed.

HIV Co-infection

There are limited data on the use of Bedaquiline fumarate (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.

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 epididymides 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

Incompatibilities

Not applicable.

Storage Conditions

Store at temperatures not exceeding 30°C.
Keep out of the sight and reach of children.
Store in the original container or package 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

Not applicable.

Instructions for Disposal

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

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patient must seek medical attention immediately at the first sign of adverse drug reaction. For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

Questions or comments? Email us at Janssendrugsafety_Phil@its.jnj.com.

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