PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

SIRTURO® 20 mg tablets.

SIRTURO® 100 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SIRTURO 20 mg tablets

Each tablet contains bedaquiline fumarate equivalent to 20 mg bedaquiline.

SIRTURO 100 mg tablets

Each tablet contains bedaquiline fumarate equivalent to 100 mg bedaquiline.

Excipients with known effect:

SIRTURO 100 mg tablets contains sugar: each tablet contains 145 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SIRTURO 20 mg tablets

Tablet.

Uncoated, white to almost white oblong tablet (12.0 mm long x 5.7 mm wide), with score line on both sides, debossed with “2” and “0” on one side and plain on other side.

The tablets may be split along the break-mark into 2 halves to facilitate dosing.

SIRTURO 100 mg tablets

Tablet.

Uncoated, white to almost white round biconvex tablet, 11 mm in diameter, 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 adult (≥ 18 years) and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg), as part of combination therapy, for pulmonary tuberculosis (TB) due to multi-drug resistant *Mycobacterium tuberculosis* in HIV negative or HIV positive who are not taking antiretrovirals.

Safety and efficacy of SIRTURO in HIV patients on treatment with antiretroviral (ARV) medicines have not been established.

Safety and efficacy of SIRTURO beyond 120 weeks have not been established.

4.2 Posology and method of administration

Posology

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 rifampicin.

Dosage – Adults (≥ 18 years)

The recommended dosage of SIRTURO for MDR-TB in adult patients is:

- Weeks 1 – 2: 400 mg once daily
- Weeks 3 – 24: 200 mg 3 times per week (with at least 48 hours between doses)

The total duration of treatment with SIRTURO is 24 weeks. Data on longer treatment duration is very limited. In patients with extensive drug resistance, where SIRTURO is considered necessary beyond 24 weeks to obtain a curative treatment, a longer duration of therapy may be considered only on a case by case basis and under close safety surveillance (see section 4.8). SIRTURO should be taken with food.

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

The recommended dosage of SIRTURO in paediatric patients (5 years to less than 18 years of age) is based on body weight and shown in Table 2.

Table 2: Recommended Dosage of SIRTURO in Paediatric Patients (5 years to less than 18 years of age)

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

a=At least 48 hours between doses

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

The prescribing medical practitioner should refer to international (e.g. WHO guidelines) and national/local TB treatment guidelines for direction on selection and duration of use of companion medicines with SIRTURO. SIRTURO should only be used in combination with at least 3 medicines to which the patient's isolate has been shown to be susceptible *in vitro*. If *in vitro* testing results are unavailable, treatment may be initiated with SIRTURO in combination with at least 4 other medicines 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 medicines in accordance with international, national/local TB treatment guidelines and local MDR-TB treatment practice. Refer to the prescribing information of the medicines used in combination with SIRTURO for their specific dosing recommendations.

Missed doses

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

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 that the total dose of SIRTURO during the 7 day period does not exceed the recommended weekly dose (with atleast 24 hours between each intake).

Do not exceed the recommended dosages.

Paediatric population (less than 5 years of age)

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

Elderly populations

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

Hepatic impairment

The pharmacokinetics of SIRTURO were assessed after single-dose administration to subjects with moderate hepatic impairment (Child-Pugh B) (see section 5.2). Based on these results, no dose adjustment is necessary for SIRTURO in patients with mild or moderate hepatic impairment.

SIRTURO has not been studied in patients with severe hepatic impairment and is not recommended in this population. (see section 4.3).

Renal impairment

SIRTURO has been mainly studied in patients with normal renal function. Renal excretion of unchanged SIRTURO is insignificant (< 0,001 %). No dose adjustment is required in patients with mild to 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).

Method of administration:

SIRTURO should be taken orally with food, as administration with food increases oral bioavailability (see section 5.2).

There are four different options for administration of SIRTURO 20 mg tablet and one method of administration of SIRTURO 100 mg tablet. Each administration method requires SIRTURO to be taken with food.

SIRTURO 20 mg tablet

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

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

Administration of 20 mg Tablets to Patients who Cannot Swallow Intact Tablets:

Dispersed in Water and Administered with Beverage or Soft Food For patients who have difficulty swallowing intact tablets, SIRTURO 20 mg tablet can be dispersed in water and administered. To aid with administration, the dispersed mixture in water can be further mixed with a beverage (e.g., water, milk product, apple juice, orange juice,

cranberry juice or carbonated beverage) or soft food (e.g., yoghurt, apple sauce, mashed banana or porridge) as follows:

- Disperse tablets in water (maximum of 5 tablets in 5 mL of water) in a drinking cup.
- Mix the contents of the cup well until the tablets are completely dispersed and then orally administer the contents of the cup immediately with food. To aid with administration, the dispersed mixture in water can be further mixed with at least 5 mL of beverage or 1 teaspoonful of soft food and then orally administer the contents of the cup immediately.
- If the total dose requires more than 5 tablets, repeat the above preparation steps with the appropriate number of additional tablets until desired dose is reached.
- Ensure no tablet residue is left in the cup, rinse with beverage or add more soft food and orally administer the contents of the cup immediately.

Crushed and Mixed with Soft Food

SIRTURO 20 mg tablet can be crushed and mixed with soft food (e.g., yogurt, apple sauce, mashed banana or porridge) immediately prior to use and administered orally. Ensure no tablet residue is left in container, add more soft food and administer the contents immediately.

Administration Through a Feeding Tube

SIRTURO 20 mg tablet can also be administered through a feeding tube (2,67 mm or greater) as follows:

- Disperse 5 tablets or less in 50 mL of non-carbonated water and mix well. Mixture should be white to almost white with visible particles expected.

- Administer through feeding tube immediately.
- Repeat with additional tablets until desired dose is reached.
- Rinse and flush with 25 mL of additional water to ensure no tablet residue is left in materials used for preparation or the feeding tube.

SIRTURO 100 mg tablet

SIRTURO 100 mg tablet should be swallowed whole with water.

4.3 Contraindications:

- Hypersensitivity to the active substance (i.e. bedaquiline) or any of the excipients listed in section 6.1
- Congenital QT prolongation
- Patients with uncontrolled cardiac dysrhythmias
- Concomitant use with medicines known to prolong the QTc interval to time intervals known to induce serious dysrhythmias
- Patients with severe hepatic impairment (Child Pugh C)

4.4 Special warnings and precautions for use

HIV-TB co-infected patients

There are no clinical data on safety and efficacy on the combined use of antiretroviral medicines and SIRTURO in HIV/MDR-TB co-infected patients and only limited clinical data on the use of SIRTURO in HIV/MDR-TB co-infected adult patients (n = 22) who were not receiving antiretroviral (ARV) therapy (see section 4.5)

There is limited information on interactions between SIRTURO (bedaquiline) and medicines that may increase or decrease bedaquiline concentrations. The use of systemic potent CYP3A4 inhibitors with SIRTURO should be avoided, as there may be an increased risk of SIRTURO associated toxicity (see section 4.5)

General

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 medicine-sensitive TB has not been established. In addition, there are no 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.

Cardiovascular safety

During clinical trials in adults with SIRTURO a prolongation of QTc interval was observed (see section 4.8). 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 (See sections 4.4 and 4.8).

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) (see section 4.3), 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, SIRTURO treatment initiation could be considered in these patients after a favourable benefit risk assessment and with frequent ECG monitoring.

SIRTURO treatment must be discontinued if the patient develops:

- **Clinically significant ventricular dysrhythmia.**
- **A QTcF interval of > 500 ms (confirmed by repeat ECG).**

An additive or synergistic effect on QT prolongation of SIRTURO when co-administered with other medicines that prolong the QT interval (including delamanid) cannot be excluded (see section 4.5).

Caution is recommended when prescribing SIRTURO concomitantly with medications with a known risk of QT prolongation. In the event that co-administration of such medicinal products with SIRTURO 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 and moxifloxacin) should be avoided.

In case of concomitant administration of SIRTURO with fluoroquinolone antibiotics that have a lower potential for significant QT prolongation (ofloxacin and levofloxacin), caution should be used.

In an open label Phase IIb 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 section 4.5). In the event that co-administration of clofazimine with SIRTURO is necessary, clinical monitoring including frequent ECG assessment is recommended.

Warnings on interactions

CYP3A4 inducers/inhibitors

SIRTURO is metabolised by CY3A4 and its exposure may therefore be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4 (see section 4.5).

Co-administration of SIRTURO and medicines that induce CYP3A4 may decrease SIRTURO plasma concentrations and reduce its therapeutic effect. Co-administration of strong CYP3A4 inducers, such as rifamycins (i.e, rifampicin; rifapentine and rifabutin) or moderate CYP3A4 inducers (i.e. efavirenz, St. John's wort, carbamazepine, etc.) used systemically should therefore be avoided during treatment with SIRTURO.

Co-administration of SIRTURO and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to SIRTURO, which could potentially increase the risk of adverse reactions. Therefore, the combination of SIRTURO and moderate or strong CYP3A4 inhibitors (such as ciprofloxacin, erythromycin, fluconazole, clarithromycin, ketoconazole, itraconazole, ritonavir) used systemically for more than 14 consecutive days should be avoided.

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). The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with SIRTURO treatment.

Hepatic safety

Increases in transaminases or aminotransferase elevations accompanied by total bilirubin ≥ 2x ULN were seen in clinical trials in adult and paediatric patients during administration of SIRTURO with the background regimen (see section 4.8). 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 medicine should be discontinued.

Other hepatotoxic medicines and alcohol should be avoided while on SIRTURO, especially in patients with diminished hepatic reserve.

Paediatric patients

In adolescents weighing between 30 and 40 kg, average exposure is predicted to be higher compared to adult patients (see section 5.2). This may be associated with an increased risk of QT prolongation or hepatotoxicity.

Lactose intolerance and lactase deficiency

SIRTURO 100 mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take SIRTURO 100 mg tablets.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction:

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

In vitro, SIRTURO 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

SIRTURO 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 SIRTURO and rifampicin in healthy adult subjects, the exposure (AUC) to SIRTURO was reduced by 52 % [90 % CI (-57; -46)]. Due to the possibility of a reduction of the therapeutic effect of SIRTURO (bedaquiline) due to a decrease in systemic exposure, co-administration of strong CYP3A4 inducers such as rifamycins (i.e. rifampicin, rifapentine and rifabutin) or moderate CYP3A4 inducers used systemically, such as efavirenz, should be avoided during treatment with SIRTURO. (see section 4.4).

Co-administration of SIRTURO and ketoconazole for 4 days in healthy adult subjects increased the exposure (AUC) to SIRTURO (bedaquiline) by 22 % [90 % CI (12; 32)] and should be avoided.

Other antimicrobial medications

The combination of SIRTURO with isoniazid/pyrazinamide in healthy adult subjects did not result in clinically relevant changes in the exposure (AUC) to SIRTURO (bedaquiline), isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with SIRTURO.

In a placebo-controlled clinical study in adult patients with MDR-TB, no major impact of co-administration of SIRTURO on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cicloserin was observed.

Antiretroviral medications

There is limited data on the interaction between SIRTURO and antiretroviral medicines.

Lopinavir/ritonavir

In an interaction study of a single dose of SIRTURO and repeated doses of lopinavir/ritonavir in adults, exposure (AUC) to SIRTURO (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).

Nevirapine

Co-administration of nevirapine in adults with a single dose of SIRTURO did not result in clinically relevant changes in the exposure to SIRTURO. Clinical data on the combined use of nevirapine and SIRTURO in HIV/MDR-TB co-infected patients are not available (see section 4.4).

QT interval prolonging medicines

There is limited information available on the potential for a pharmacodynamic interaction between SIRTURO and medicines that prolong the QT interval. In a medicine interaction study of SIRTURO (bedaquiline) and ketoconazole in adults, a greater effect on QTc was observed after repeated dosing with SIRTURO and ketoconazole in combination than after repeated dosing with the individual medicines. An additive or synergistic effect on QT prolongation of SIRTURO when co-administered with other medicines that prolong the QT interval cannot be excluded (see section 4.4).

QT interval and concomitant clofazimine use

In an open label Phase IIb trial in adults, mean increases in QTcF were larger in the 17 subjects who were using clofazimine at week 24 (mean change from reference of 31,9 ms) than in subjects who were not using clofazimine at week 24 (mean change from reference of 12,3 ms). (see section 4.4).

Paediatric population

Medicine interaction studies have only been performed in adults.

It is assumed that there would be similar medicine interactions in the paediatric population and similar cautions should apply for all medications stated above.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Breastfeeding

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

In rats, concentrations of SIRTURO 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.

Women using SIRTURO should not breastfeed their infants.

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 SIRTURO have been performed. Patients should be advised not to drive or operate machinery if they experience dizziness while taking SIRTURO.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions from clinical trials in adult patients

Adverse drug reactions (ADRs) for SIRTURO were identified from pooled Phase IIb clinical trial data (both controlled and uncontrolled) containing 335 patients who received SIRTURO in combination with a background regimen of TB medicines. 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 I and Phase IIa 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. Refer to the prescribing information of the medicines used in combination with SIRTURO for their respective adverse reactions.

Tabulated list of adverse reactions

Adverse drug reactions to SIRTURO reported from controlled trials in 102 patients treated with 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: Adverse drug reactions from controlled trials during treatment with SIRTURO		
System Organ Class (SOC)	**Frequency category**	**ADRs**
Nervous system disorders	Very common	Headache, dizziness
Cardiac disorders	Common	ECG QT prolonged
Gastrointestinal disorders	Very common Common	Nausea, vomiting Diarrhoea
Hepatobiliary disorders	Common	Increased transaminases*
Musculosketal and connective tissue disorders	Very common Common	Arthralgia Myalgia

*Terms represented by “increased transaminases” included, AST increased, ALT increased, hepatic enzyme increased and abnormal hepatic function

No additional ADRs were identified in adult patients from the uncontrolled study (n=233) nor from the Phase I and II studies.

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

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

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

The trial was designed to enrol patients from 12 years to less than 18 years of age (15 patients aged 14 years to less than 18 years were Enrolled) with confirmed or probable MDR-TB infection who received SIRTURO (400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks) in combination with a background regimen (see Pharmacological properties – Clinical Studies). The most common adverse drug reactions were arthralgia in 6/15 (40%) patients and nausea in 2/15 (13%) patients. Among the 15 adolescent patients, no deaths occurred during treatment with SIRTURO. Observed laboratory abnormalities were comparable to those in adults. No new adverse drug reactions were identified compared to those seen in adults.

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

The trial was designed to enrol patients from 5 years to less than 12 years of age (15 patients aged 5 years to less than 11 years were Enrolled) with confirmed or probable MDR-TB infection who received SIRTURO (200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks) in combination with a background regimen (see *Pharmacological properties – Clinical Studies*).

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

Deaths:

In the randomised phase IIb C208 study in adult patients a higher rate of deaths was seen in the SIRTURO treatment group 12,7 % (10/79) compared to the placebo treatment group 3,7 % (3/81). One death in the SIRTURO group and one death in the placebo group were reported after the week 120 window. In the SIRTURO group, all of the five deaths due to tuberculosis occurred in patients whose sputum culture status at last visit was 'not converted'. The causes of death in the remaining SIRTURO subjects were alcohol poisoning, hepatitis/hepatic cirrhosis, septic shock/peritonitis, cerebrovascular accident and motor vehicle accident. One of the ten deaths in the SIRTURO group (due to alcohol poisoning) occurred during the 24-week treatment period. The other nine deaths among those treated with SIRTURO occurred after completion of treatment with this agent (range 86-911 days post-SIRTURO; median 344 days). The observed imbalance in deaths between the two treatment groups is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other medicinal products used to treat tuberculosis, human immunodeficiency virus status, or severity of disease could be observed. During the trial, there was no evidence of antecedent significant QT prolongation or clinically significant dysrhythmia in any of the patients that died.

In the open-label C209 trial, 6,9 % (16/23) 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.

Adverse events of special interest

Cardiovascular

In the controlled Phase IIb 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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose:

Cases of intentional or accidental acute overdose with SIRTURO were not reported during clinical trials. In a study of 44 healthy adult subjects receiving a single 800 mg dose of SIRTURO, adverse reactions were consistent with those observed in clinical studies at the recommended dose (see section 4.8).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 20.2.3 Tuberculostatics

Mechanism of action:

Bedaquiline is a diarylquinoline which 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.

Pharmacodynamic effects:

Bedaquiline is a diarylquinoline with *in vitro* activity against medicine-sensitive TB (DS-TB), MDR–TB including pre-extensively medicine 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) rifampicin and (3) either a fluoroquinolone or at least one of three injectable second-line medicines (amikacin, capreomycin or kanamycin).

XDR-TB is defined as *in vitro* resistance of the patient's isolate to: (1) isonaizid, (2) rifampicin, (3) a fluoroquinolone and (4) at least one of three injectable second-line medicines (amikacin, capreomycin or kanamycin).

Bedaquiline demonstrates selectivity for mycobacterial (prokaryotic) ATP synthase as opposed to mammalian (eukaryotic) ATP synthase. Bedaquiline has low activity for human ATP synthase in mitochondria (IC_{50} > 100 µM), resulting in a selectivity index of > 10 000 compared to the mycobacterial ATP synthase (IC_{50} 0,01 µM).

Bedaquiline has activity against *M. tuberculosis* with a minimum inhibitory concentration (MIC) for medicine-sensitive as well as medicine-resistant strains (MDR including pre-XDR, XDR-strains) in the range of ≤ 0,008 – 0,12 µg/mL. Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of *N*-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23 % to 31 %) in humans and lower antimycobacterial activity (4- 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 sterilising activities.

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 4,0 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 0,50 micrograms/mL. Isolates with efflux-based mutations are also less susceptible to clofazimine.

Commonly susceptible species

Mycobacterium tuberculosis

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 dose 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 very low.

Biotransformation:

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. The long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.

Special populations:

Patients with hepatic impairment:

After single-dose administration of SIRTURO to 8 subjects with moderate hepatic impairment (Child-Pugh B), exposure to bedaquiline and M2 ($AUC_{672\,h}$) 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).

Patients with renal impairment:

SIRTURO has been mainly 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 dose 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 medicine 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.

Paediatric patients (less than 18 years of age)

Paediatric patients (12 years to less than 18 years of age)

The pharmacokinetics of bedaquiline and its major metabolite N-monodesmethyl bedaquiline (M2) in 15 adolescent patients 14 years to less than 18 years of age with MDR-TB receiving SIRTURO (400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks) in combination with a background regimen were comparable to those in adult patients with MDR-TB using the same dose regimen. There was no impact of body weight on bedaquiline pharmacokinetics in adolescent patients in trial C211 (38 to 75 kg), similar to what was observed in adults.

In adolescents weighing between 30 and 40 kg, average exposure is predicted to be higher compared to adult patients. This may be associated with an increased risk of QT prolongation or hepatotoxicity

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

The pharmacokinetics of bedaquiline and its major metabolite M2 in 15 Paediatric patients 5 years to less than 11 years of age (body weight: 14 to 36 kg) with MDR TB receiving SIRTURO (200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks) in combination with a background regimen were comparable to those in adult patients with MDR TB using the adult dose regimen.

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

An integrated population pharmacokinetic analysis demonstrated that the bedaquiline exposure in patients 5 years to less than 18 years for the recommended weight-based dosing regimen (Table 2) is similar to adult patients.

Paediatric patients (less than 5 years of age)

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

Elderly patients:

There is limited 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.

Race

In a limited 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. There are insufficient clinical data to determine whether lower exposure has a significant effect on the efficacy of bedaquiline in this population. This low exposure was not considered 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.

HIV co-infection

There are no data on the use of SIRTURO in HIV co-infected patients treated with antiretroviral medicines (see section 4.4).

Clinical Efficacy and safety:

A placebo-controlled, double-blind, randomised trial (C208) was conducted in newly diagnosed patients with multi-drug resistant pulmonary *Mycobacterium tuberculosis*. Patients were randomised to receive treatment with either SIRTURO and other medicines used to treat MDR-TB (SIRTURO treatment group) (n = 79) or placebo plus other medicines used to treat MDR - TB (placebo treatment group) (n = 81); the other medicines used to treat MDR-TB consisted of a combination of 5 other antimycobacterial medicines (ethionamide, kanamycin, pyrazinamide, ofloxacin, and cicloserin/terizidone or available alternative). 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: sixty three percent of the population was male, with a median age of 34 years, 35 % were Black, and 15 % were HIV-positive. Most patients (73,7 %) had cavitary disease.

SIRTURO was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times per week for the following 22 weeks. After the 24-week study medicine (SIRTURO or placebo) treatment phase, patients continued to receive their other medicines used to treat MDR-TB until a total treatment duration of 18 to 24 months was achieved, or at least 12 months after the first confirmed negative culture.

Time to sputum culture conversion was defined as the interval in days between the first dose of study medicine and the date of the first of two consecutive negative sputum cultures collected at least 25 days apart during treatment. In this ongoing trial, the SIRTURO treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 24. Table 1 shows the proportion of patients with sputum culture conversion after 24 weeks of treatment with SIRTURO or placebo in combination with other medicines used to treat MDR-TB (with patients who discontinued considered as failures).

Table 1: Culture conversion status

Culture Conversion Status [a] **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[b] 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[c] **	*6 (9,1 %)*	10 (15,2 %)
Discontinued but converted	*11 (16,7 %)*	*12 (18,2 %)*

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

[b] * Patients who died during the trial or discontinued the trial were considered as non-responders.

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

Study C209 evaluates the safety, tolerability, and efficacy of 24 weeks treatment with open-label SIRTURO as part of an individualised treatment regimen in 233 patients who were sputum smear positive within 6 months prior to screening. This study included patients of all three resistance categories (MDR -, pre-XDR- and XDR-TB).

The primary efficacy endpoint was the time to sputum culture conversion during treatment with SIRTURO (median 57 days, for 205 patients with sufficient data). At week 24, sputum culture conversion was seen in 163/205 (79,5 %) patients. Conversion rates at week 24 were highest (87,1 %; 81/93) in patients with MDR -TB, 77,3 % (34/44) in pre-XDR-TB patients and lowest 54,1 %; 20/37) in XDR-TB patients. Extent of resistance based on central laboratory medicine susceptibility testing results was not available for 32 subjects in the mITT population. These subjects were excluded from the subgroup analysis by extent of resistance of *Mycobacterium tuberculosis* strain.

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 medicines (*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 backgound regimen was continued) occurred in 9 patients (21,4 %) and was maintained at week 120.

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.

Clinical study evaluating the QTc interval.

An increase in QTcF when using SIRTURO was demonstrated in Phase II studies (see section 4.4).

Paediatric population:

Paediatric patients (5 years to less than 18 years of age)

The pharmacokinetics, safety and tolerability of SIRTURO in combination with a background regimen were evaluated in trial C211, a single-arm, open-label, multi-cohort Phase 2 trial that was designed to enrol 30 paediatric patients 5 years to less than 18 years of age with confirmed or probable MDR-TB infection who were to complete at least 24 weeks of treatment.

Paediatric patients (12 years to less than 18 years of age)

Fifteen adolescent patients were Enrolled in this cohort. SIRTURO was administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks using the 100 mg tablet. These 15 patients had a median age of 16 years (range: 14-17), weighed 38 kg to 75 kg, and were 80% female, 53% Black, 33% White and 13% Asian.

In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 75% (6/8 microbiologically evaluable patients) at week 24.

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

Fifteen paediatric patients were Enrolled in this cohort. SIRTURO was administered as 200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks using the 20 mg tablet. These 15 patients had median age of 7 years (range: 5-10), weighed 14 kg to 36 kg, and were 60% female, 60% Black, 33% White and 7% Asian. In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 100% (3/3 microbiologically evaluable patients) at Week 24.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

SIRTURO 20 mg Tablets:

Colloidal anhydrous silica

Crospovidone

Hypromellose 2910 5 mPa.s

Polysorbate 20

Purified water (removed during processing)

Silicified microcrystalline cellulose

Sodium stearyl fumarate

SIRTURO 100 mg Tablets:

Lactose (as monohydrate).

Hypromellose 2910 15 mPa.s.

Polysorbate 20.

Purified water (removed during processing).

Microcrystalline cellulose.

Croscarmellose sodium.

Colloidal anhydrous silica.

Magnesium stearate.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

Tablets packaged in:

SIRTURO 20 mg tablets

High density polyethylene (HDPE) bottles, stored at or below 25 ° C: 3 years.

SIRTURO 100 mg tablets

- Aluminium/aluminium foil blisters, stored at or below 25 ° C : 3 years
- High density polyethylene (HDPE) bottles, stored at or below 25 ° C: 3 years.

6.4 Special precautions for storage:

SIRTURO 20 mg tablets

Store at or below 25 ºC.

Store in original package and keep the container tightly closed to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

SIRTURO 100 mg tablets

Store at or below 25 ºC.

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

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:

20 mg tablets

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

100 mg tablets

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

OR

An aluminium/aluminium blister with heat seal coating. Each packaging contains one or more blister(s) of six (6) tablets.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty.) Ltd.

(Reg No.: 1980/011122/07)

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8. REGISTRATION NUMBERS

SIRTURO 100 mg Tablets: 47/20.2.3/1182

SIRTURO 20 mg Tablets: 56/20.2.3/0799

9. DATE OF FIRST AUTHORISATION

Date on the registration certificate:

SIRTURO 100 mg Tablets: 02 August 2014

SIRTURO 20 mg Tablets: 04 July 2023

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA:

04 July 2023