# SIRTURO®

## Bedaquiline

## NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

SIRTURO 100 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

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

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

## 3. PHARMACEUTICAL FORM

Tablet.

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

SIRTURO is indicated as part of combination therapy in adult (≥ 18 years) and paediatric patients (12 years to less than 18 years of age and weighing at least 30 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid.

### 4.2 Dose and method of administration

SIRTURO should only be administered as part of a regimen for the treatment of pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid. It is recommended that SIRTURO is administered by directly observed therapy (DOT).

The prescribing physician should refer to international (e.g. WHO guidelines) and national/ local TB treatment guidelines for direction on selection and duration of use of companion drugs with SIRTURO. SIRTURO should only be used in combination with at least 3 drugs to which the patient's isolate has been shown to be susceptible *in vitro*. If *in vitro* drug susceptibility testing results are unavailable, treatment may be initiated with SIRTURO in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible.

Throughout treatment with SIRTURO, patients should take their companion drugs in accordance with international, national/local TB treatment guidelines. Refer to the prescribing information of the drugs used in combination with SIRTURO for their specific dosing recommendations.

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

The recommended dosage of SIRTURO in adult and paediatric patients (12 years to less than 18 years of age) is shown in Table 1.

**Table 1: Recommended dosage of SIRTURO**

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

SIRTURO 100 mg tablet should be swallowed whole with water and taken with food.

## Treatment duration

The total duration of treatment with SIRTURO is 24 weeks. When treatment with SIRTURO is considered necessary beyond 24 weeks, treatment may be continued up to 40 weeks in adults, at a dose of 200 mg three times per week (see **section 5 Pharmacological properties – Clinical efficacy and safety**).

## Missed dose(s)

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

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

From Week 3 onwards, if a dose is missed, patients should take the missed dose, and adjust the dosing schedule to ensure the total dose of SIRTURO during the 7 day period does not exceed 600 mg (taken as 3 intakes of 200 mg per day, at least 24 hours apart).

## Special populations

***Paediatrics (less than 12 years of age)***

The safety and efficacy of SIRTURO in children less than 12 years of age or weighing less than 30 kg have not been established.

***Elderly (65 years of age and older)***

There are limited clinical data on the use of SIRTURO in elderly patients (see **section 5.2 Pharmacokinetic Properties – Special populations**).

***Renal impairment***

SIRTURO has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is insignificant (< 0.001%). No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis, SIRTURO should be used with caution (see **section 5.2 Pharmacokinetic Properties – Renal impairment**).

***Hepatic impairment***

The pharmacokinetics of bedaquiline were assessed after single-dose administration to adults with moderate hepatic impairment (Child-Pugh B) (see **section 5.2 Pharmacokinetic Properties – Hepatic impairment**). Based on these results, no dose adjustment is necessary for SIRTURO in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

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

### Resistance to bedaquiline

Bedaquiline must only be used in an appropriate combination regimen for the treatment of pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid as recommended by official guidelines, such as from WHO, to reduce the risk of development of resistance to bedaquiline (see **section 4.2 Dose and method of administration**).

### QT prolongation

SIRTURO may prolong the QT interval (see **section 4.8 Undesirable effects**). An ECG should be obtained prior to and after initiation of therapy with SIRTURO to monitor the QTc interval. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected.

The following may increase the risk for QT prolongation:

- Heart failure
- QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat ECG)
- 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 favourable benefit-risk assessment and with frequent ECG monitoring.

When co-administering SIRTURO and other drugs that prolong the QT interval (including clofazimine, delamanid or fluoroquinolones), an additive effect on QT prolongation is expected (see **section 4.5 Interactions with other medicines and other forms of interactions**). Treatment with SIRTURO may be considered after a favourable benefit-risk assessment and with ECG monitoring.

Treatment with SIRTURO must be discontinued if the patient develops:

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

## Hepatic safety

Increases in transaminases 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 Undesirable effects**). Patients should be monitored during treatment. If AST or ALT exceeds 5 times the upper limit of normal, the regimen should be reviewed and SIRTURO and/or any hepatotoxic background drug(s) should be discontinued.

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

# 4.5 Interactions with other medicines and other forms of interaction

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

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

## CYP3A4 inducers

Bedaquiline is metabolized by CYP3A4.

Co-administration of bedaquiline with moderate or strong CYP3A4 inducers decreases bedaquiline plasma concentrations and may reduce the therapeutic effect of SIRTURO. Co-administration of moderate or strong CYP3A4 inducers used systemically, such as efavirenz and rifamycins (i.e., rifampicin, rifapentine and rifabutin) should therefore be avoided during treatment with SIRTURO.

In an interaction study of single-dose bedaquiline and once-daily rifampicin, a strong CYP3A4 inducer, in healthy adults, bedaquiline exposure (AUC) 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 moderate and strong CYP3A4 inducers, such as efavirenz and rifamycins (i.e., rifampicin, rifapentine and rifabutin) should be avoided during treatment with SIRTURO.

Coadministration of multiple-dose nevirapine, a weak CYP3A4 inducer, in adults did not result in clinically relevant changes in the exposure of bedaquiline. In the Phase 3 study, coadministration of nevirapine and SIRTURO as part of combination therapy for up to 40 weeks in patients coinfected with HIV resulted in a 30% [95% CI (0%; 60%)] decrease in bedaquiline exposure (AUC) with no associated reduction in therapeutic effect. Therefore no dose adjustment is needed when co-administering SIRTURO with weak CYP3A4 inducers.

## CYP3A4 inhibitors

Co-administration of SIRTURO and CYP3A4 inhibitors does not have a clinically relevant effect on bedaquiline exposure. Therefore, the coadministration of SIRTURO and CYP3A4 inhibitors is allowed, and no dose adjustment is needed.

In healthy adults, co-administration of clarithromycin and single-dose SIRTURO increased the mean [90% CI] bedaquiline exposure (AUC) by 14% [9%; 19%].

In the Phase 3 study, long-term co-administration of SIRTURO as part of a combination therapy and lopinavir/ritonavir in patients coinfected with HIV resulted in a 20% increase of bedaquiline exposure at Week 24 [95% CI (-10%; 60%)] and no dose adjustment is required.

## Other Antimycobacterial medications

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

impact of co-administration of SIRTURO on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

### QT interval prolonging drugs

In an open-label Phase 2b trial in adults, additive increases in QTcF were observed in the 17 patients who were using concomitant clofazimine at Week 24 (mean change from reference QTcF 31.9 ms compared to 12.3 ms in patients who were not using concomitant clofazimine).

In the Phase 3 trial, additive increases in QTcF were observed when combining clofazimine and levofloxacin with SIRTURO.

In an interaction study of bedaquiline and ketoconazole in healthy adults, a greater effect on QTcF was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual drugs (see **section 4.4 Special warnings and precautions for use**).

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

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

### 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.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for SIRTURO and any potential adverse effects on the breastfed infant from 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.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of bedaquiline based on the

comprehensive assessment of the available adverse event information. A causal relationship with bedaquiline cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Refer to the prescribing information of the drugs used in combination with SIRTURO for their respective adverse reactions.

## Adverse reactions from clinical trials in adult patients

Adverse reactions for SIRTURO were identified from Phase 2b clinical trial data (both controlled and uncontrolled) in 335 patients who received SIRTURO for 8 weeks or 24 weeks. No new adverse reactions were identified in the Phase 3 active-controlled trial including 354 patients who received SIRTURO for 40 weeks or 28 weeks. In these studies, patients received SIRTURO in combination with other antimycobacterial drugs.

The most frequent adverse reactions (> 10.0% of patients) reported during treatment with SIRTURO in the Phase 3 trial were QT prolongation, nausea, vomiting, arthralgia, transaminases increased, dizziness and headache. Adverse reactions with SIRTURO in combination with other antimycobacterial drugs in the 40-week arm versus those in the 40-week active control arm are presented in **Table 2**. Adverse 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 Reactions During Treatment with SIRTURO in the Phase 3 Trial (STREAM Stage 2)**

| Adverse Reactions | Frequency | SIRTURO[a] N=211 n (%) | Active Control[b] N=202 n (%) |
|---|---|---|---|
| **Nervous system disorders** | | | |
| Dizziness | Very common | 37 (18) | 42 (21) |
| Headache | Very common | 36 (17) | 36 (18) |
| **Gastrointestinal disorders** | | | |
| Nausea | Very common | 114 (54) | 127 (63) |
| Vomiting | Very common | 113 (54) | 125 (62) |
| Diarrhea | Common | 12 (6) | 17 (8) |
| **Hepatobiliary disorders** | | | |
| Transaminases increased[c,d] | Very common | 63 (30) | 59 (29) |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthralgia | Very common | 94 (45) | 67 (33) |
| Myalgia | Common | 19 (9) | 6 (3) |
| **Investigations** | | | |
| ECG QT prolonged[e] | Very common | 128 (61) | 113 (56) |

[a] 40-week, all-oral treatment of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)

[b] 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid, and prothionamide in the first 16 weeks (intensive phase)

[c] Terms represented by 'transaminases increased' included AST increased, ALT increased, hepatic enzyme increased, hepatic function abnormal, hypertransaminasemia, and transaminases increased

[d] Incidence of transaminases increased in the controlled Phase 2b study was Common (6.9% in the SIRTURO arm and 1% in placebo control)

[e] Incidence of QT prolonged in Phase 2b study was Common (2.9% in the SIRTURO arm and 3.8% in placebo control)

In the 28-week SIRTURO-containing arm, in which SIRTURO was used in combination with other antimycobacterial drugs, the most common adverse reactions (greater than 10%) were QT prolongation (56%), arthralgia (55%), and nausea (43%), vomiting (29%), transaminase increased (21%), dizziness (21%), and headache (16%).

## QT prolongation

In clinical trials in adult patients treated with SIRTURO, collectively these studies show a mild (< 10 ms) QTcF increase throughout treatment attributable to M2, the major bedaquiline metabolite. In combination with other QT-prolonging drugs (e.g., clofazimine, delamanid, or

fluoroquinolones), a prolongation of the QTc interval not more than additive was observed (see **section 4.5 Interactions with other medicines and other forms of interactions**).

In the controlled Phase 2b study, 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 (at Week 18) in QTcF during the 24 weeks of treatment with SIRTURO was 15.7 ms, compared to 6.2 ms in the placebo group. After treatment with SIRTURO ended, the QTcF gradually decreased, and the mean value was similar to that in the placebo group by study Week 60 (see **section 4.4 Special warnings and precautions for use**).

In the controlled Phase 3 study, in which SIRTURO and active control treatment arms included both clofazimine and a fluoroquinolone, the mean QTcF gradually increased from baseline over the first 10 to 14 weeks, when a plateau was reached and additive QT prolongation was observed. The highest mean QTcF increase from baseline was 34.5 ms for the SIRTURO-containing arm and 29.9 ms for the non-SIRTURO-containing control. Throughout treatment, mean QTcF increase was less than 10 ms higher in the SIRTURO-containing arm compared to the control. Upon treatment completion mean QTcF decreased steadily. QTcF values ≥500 ms were observed in 5.2% of patients in the SIRTURO-containing arm compared to 7.4% in the non-SIRTURO-containing control arm (see **section 4.4 Special warnings and precautions for use**).

### Adverse reactions from a clinical trial in paediatric patients (12 years to less than 18 years of age)

The safety assessment of bedaquiline is based on the Week 120 analysis of the ongoing single-arm, open-label Phase 2 trial (C211) in 15 adolescent patients. The trial was designed to enrol patients from 12 years to less than 18 years of age from (patients 14 years to less than 18 years of age were enrolled) with confirmed or probable TB due to *M. tuberculosis* resistant to at least rifampicin 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 **section 5 Pharmacological properties – Clinical efficacy and safety**).

The most common adverse reactions were arthralgia in 6/15 (40%) patients and nausea in 2/15 (13%) patients. Observed laboratory abnormalities were comparable to those in adults. No new adverse reactions were identified compared to those seen in adults. No deaths were reported during the study.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

## 4.9 Overdose

### Symptoms and signs

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

### Treatment

There is no experience with the treatment of acute overdose with SIRTURO. General measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) monitoring should be taken in case of deliberate or accidental overdose. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma. Clinical monitoring should be considered.

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

Bedaquiline is a diarylquinoline with *in vitro* activity against *Mycobacterium tuberculosis* complex strains with sensitivity to rifampicin and isoniazid and *Mycobacterium tuberculosis* complex strains resistant to at least rifampicin and isoniazid.

## 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).

Bedaquiline has activity against *M. tuberculosis* with a minimal inhibitory concentration (MIC) for drug-sensitive as well as drug-resistant strains in the range of ≤ 0.008 to 0.25 µg/mL. Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (3- to 6-fold lower) compared to the parent compound.

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

## 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 µg/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 µg/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 microbiological outcomes is unclear because of the low incidence of such cases in the Phase 2 and Phase 3 trials.

### *Lists of microorganisms*

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

### *Susceptibility test methods*

When available, the clinical microbiology laboratory should provide the physician with the *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 antimycobacterial drug products for treatment.

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

**Table 3. Susceptibility Test Result Interpretive Criteria for Bedaquiline**

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

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

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

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

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

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

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

## Effect on QT/QTc interval and cardiac electrophysiology

The effect of a single supratherapeutic bedaquiline 800 mg dose on QTc interval was evaluated in a double-blind, randomised, placebo-, and positive-controlled (moxifloxacin 400 mg) parallel group QT study in 44 healthy adults. The placebo-adjusted maximum mean increase in QTcF was 5.2 ms, 90% confidence interval [90% 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. For data on QT prolongation in patients treated with repeated dosing in clinical trials, see **section 4.8 Undesirable effects**.

## Clinical efficacy and safety

## Adult patients

### C208

A Phase 2b, placebo-controlled, double-blind, randomised trial (C208) was conducted to evaluate the antimycobacterial activity, safety, and tolerability of SIRTURO in newly diagnosed patients with sputum smear-positive pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid, including patients with resistance to second-line injectables or fluoroquinolones. Patients were randomised to receive treatment with either SIRTURO (N = 79) or placebo (N = 81) for 24 weeks in combination with a preferred 5-drug background regimen consisting of ethionamide (ETH), kanamycin (KAN), pyrazinamide (PZA), ofloxacin (OFL), and cycloserine/terizidone. 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 24-week investigational period, the background regimen was continued to complete 18 to 24 months of total 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, the majority (35% [N = 56]) were Black and 15% (N = 24) of patients were HIV-positive. Most patients had cavitation in one lung (57.5%); cavitation in both lungs was observed in 16.3% of patients. For patients in the mITT population with full characterisation of resistance status, 76% (85/112) were infected with a *M. tuberculosis* strain resistant to rifampicin and isoniazid and 24.1% (27/112) were infected with a *M. tuberculosis* strain also resistant to second-line injectables or fluoroquinolones.

The primary outcome parameter was the time to sputum culture conversion (i.e. the interval in days between the first SIRTURO intake and the date of the first of two consecutive negative mycobacteria growth indicator tube (MGIT) cultures from sputum collected at least 25 days apart) during treatment with SIRTURO or placebo.

The addition of SIRTURO to a preferred background regimen resulted in a decreased time to culture conversion and improved culture conversion rates compared to placebo. Median time to culture conversion according to the primary analysis method was 83 days for the SIRTURO group compared to 125 days for the placebo group ($p < 0.0001$; hazard ratio, [95% CI 2.44 (1.57; 3.80)]. The proportion of patients in the modified intent-to-treat (mITT) population with sputum culture conversion after 24 weeks of treatment with SIRTURO or placebo in combination with background regimen (with patients who discontinued considered as non-responders), was 52/66 (78.8%) in the SIRTURO group and 38/66 (57.6%) in the placebo group. In the SIRTURO group, no or only minor differences in time to culture conversion and culture conversion rates were observed between patients with TB infected with *M. tuberculosis* resistant to rifampicin, isoniazid and second-line injectables or fluoroquinolones and patients with TB due to *M. tuberculosis* resistant to only rifampicin and isoniazid. The rates of culture conversion in patients with *M. tuberculosis* strains resistant only to rifampicin and isoniazid were 82.1% (32/39) in the SIRTURO group and 62.2% (28/45) in the placebo group. In addition, in the subgroup of patients infected with *M. tuberculosis* also resistant to either second-line injectables or fluoroquinolones, a higher rate of culture conversion was seen in the SIRTURO group [73.3% (11/15)] vs the placebo group [33.3% (4/12)].

Durability of response seen in the SIRTURO treatment group was supported by the results shown below in Table 4. The proportion of responders (with patients who discontinued considered as non-responders) at Week 120 was 41/66 (62.1%) in the SIRTURO group and 29/66 (43.9%) in the placebo group.

During the trial, 12.7% (10/79) patients died in the SIRTURO treatment group (N=79) compared to 3.7% (3/81) patients in the placebo group (N=81). One death occurred during administration of SIRTURO. The median time to death for the remaining nine patients was 344 days after last intake of SIRTURO. In the SIRTURO treatment group, the most common cause of death as reported by the investigator was TB (5 patients). The causes of death in the remaining patients treated with SIRTURO varied. During the trial, there was no evidence of antecedent significant QTcF prolongation or clinically significant dysrhythmia in any of the patients who died.

**Table 4: Culture conversion Status in C208**

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

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

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

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

**C209**

A Phase 2b, open-label trial (C209) was conducted to evaluate the safety, tolerability, and efficacy of SIRTURO as part of an individualized treatment regimen in 233 patients with sputum smear positive (within 6 months prior to screening) pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid. 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 a strain resistant to isoniazid and rifampicin, 25.3% (44/174) of patients were infected with a strain also resistant to second-line injectables or fluoroquinolones, and 21.3% (37/174) of patients were infected with a strain also resistant to second-line injectables and fluoroquinolones.

Patients received SIRTURO for 24 weeks in combination with an individualized background regimen of antimycobacterial 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%). SIRTURO was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times/week for the following 22 weeks. Upon completion of the 24-week treatment with SIRTURO, all patients continued to receive their background regimen in accordance with national/local TB program (NTP) treatment guidelines.

The primary efficacy endpoint was the time to sputum culture conversion during treatment with SIRTURO. Median time to sputum culture conversion excluding patients with drug–sensitive TB (DS-TB) and those that did not have a positive sputum culture at screening and/or baseline (mITT; 205 patients), was 57 days. At Week 24, 163 of 205 (79.5%) patients responded to SIRTURO treatment as determined by sputum culture conversion rates. Conversion rates at Week 24 were highest (87.1%; 81/93) in patients with *M. tuberculosis* isolates resistant to only rifampicin and isoniazid, 77.3% (34/44) in patients with pulmonary TB due to *M. tuberculosis* resistant to rifampicin, isoniazid, second-line injectables or fluoroquinolones, and lowest (54.1%; 20/37) in patients with *M. tuberculosis* isolates resistant to rifampicin, isoniazid, second-line injectables and fluoroquinolones.

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 *M. tuberculosis* isolates resistant to only rifampicin and isoniazid, 70.5% (31/44) in patients with pulmonary TB due to *M. tuberculosis* resistant to rifampicin, isoniazid, second-line injectables or fluoroquinolones, and lowest (62.2%; 23/37) in patients with *M. tuberculosis* isolates resistant to rifampicin, isoniazid, second-line injectables and fluoroquinolones.

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.

In the open-label C209 trial in adult patients, 6.9% (16/233) of patients died. The most common cause of death as reported by the investigator was TB (9 patients). Eight of nine patients who died of TB had not converted or had relapsed. The causes of death in the remaining patients varied.

**STREAM Stage 2**

A Phase 3, open-label, multicentre, active-controlled, randomised trial (STREAM Stage 2) was conducted to evaluate the efficacy and safety of SIRTURO coadministered with other oral anti-TB drugs for 40 weeks in patients with sputum smear-positive pulmonary TB caused by *M. tuberculosis* that was resistant to at least rifampicin. Patients in whom the *M. tuberculosis* strain was known to be resistant at screening to second-line injectable agents or fluoroquinolones were excluded from enrolment. When phenotypic susceptibility testing of the baseline isolates became available post randomisation, patients infected with *M. tuberculosis* resistant to either second-line injectable agents or fluoroquinolones were kept in the study, however those with *M. tuberculosis* resistant to both second-line injectables and fluoroquinolones were discontinued.

Patients were randomised to one of four treatment arms:

- Arm A (N=32), the locally used treatment in accordance with 2011 WHO treatment guidelines with a recommended 20-month duration
- Arm B (N=202), a 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid, and prothionamide in the first 16 weeks (intensive phase)

- Arm C (N=211), a 40-week, all-oral treatment of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)

- Arm D (N=143), a 28-week treatment consisting of SIRTURO, levofloxacin, clofazimine, and pyrazinamide supplemented by kanamycin injectable and a higher isoniazid dose for the first 8 weeks (intensive phase)

SIRTURO was administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 38 weeks (in Arm C) or 26 weeks (in Arm D).

All patients were to be followed until study completion at Week 132. During study conduct, enrolment in Arms A and D was stopped due to changes in the standard of care for TB treatment. Patients already randomised to these study arms were to complete their assigned treatment and follow-up.

The primary objective was to assess whether the proportion of patients with a favourable efficacy outcome in Arm C was noninferior to that in Arm B at Week 76. The safety and efficacy of Arm D were included as secondary objectives. Enrolment in Arm A was limited and outcome for this study arm is not described below.

The primary efficacy outcome measure was the proportion of patients with a favourable outcome at Week 76. A favourable outcome at Week 76 was defined as last 2 consecutive cultures negative and no unfavourable outcome. An unfavourable outcome at Week 76 was assessed as a composite endpoint covering both clinical and microbiological aspects such as changes in treatment, all-cause mortality, at least 1 of the last 2 culture results positive, or no culture results within the Week 76 window. In case of treatment failure, recurrence or serious toxicity on the allocated treatment, salvage treatment that could include SIRTURO was provided based on investigator judgment.

In the overall study population (N=588), 59.9 % were male, median age was 32.7 years, 47.3% were Asian, 36.6% were Black, 16.2% were White and 16.5% were HIV-coinfected. Most patients had cavitation (73.1%), with multiple cavities in 55.3% of patients. Of the 543 patients in the primary efficacy population (mITT population, defined as patients with a positive culture for *M. tuberculosis* at screening or randomisation), 100% of the patients' *M. tuberculosis* isolates were resistant to rifampicin, 12.5% had resistance to rifampicin while susceptible to isoniazid, 76.4% had resistance to at least rifampicin and isoniazid, and 11% had resistance to rifampicin, isoniazid and either second-line injectables or fluoroquinolones.

For the efficacy analyses beyond Week 76, data collection was stopped at the point when the last recruited patient was projected to reach Week 96. The long-term efficacy data therefore include data up to at least Week 96 for all patients, and up to Week 132 for 146/196 (74.5%) patients in Arm C and 145/187 (77.5%) patients in Arm B.

Table 5 shows results for favourable and unfavourable outcomes at Week 76 and Week 132 in the Phase 3 trial.

**Table 5: Treatment Outcome in STREAM Stage 2 (Phase 3 Trial)**

| | mITT population | |
|---|---|---|
| | **SIRTURO[a] (N=196)** | **Active Control[b] (N=187)** |
| **Favourable outcome at Week 76 n (%)** | 162 (82.7) | 133 (71.1) |
| Difference[c] SIRTURO[a] vs Active Control[b] (95% CI) | 11.0% (2.9%, 19.0%) | |
| Superiority p-value | 0.004 | |
| **Unfavourable outcome at Week 76 n (%)** | 34 (17.3) | 54 (28.9) |
| Reasons for unfavourable outcome through Week 76[d] | | |
| Treatment modified or extended | 16 (8.2) | 43 (23.0) |
| No culture results within Week 76 window | 12 (6.1%) | 7 (3.7) |
| Death through Week 76 | 5 (2.6) | 2 (1.1) |
| At least one of last 2 cultures positive at Week 76 | 1 (0.5) | 2 (1.1) |
| **Favourable outcome at Week 132[e] n (%)** | 154 (78.6) | 129 (69.0) |
| Difference[c] SIRTURO[a] vs Active Control[b] (95% CI) | 9.0% (0.6%,17.5%) | |

mITT = modified intent-to-treat

[a] Arm C 40-week, all-oral regimen of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)

[b] Arm B 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high dose isoniazid and prothionamide in the first 16 weeks (intensive phase)

[c] The adjusted difference in proportions was estimated using a stratified analysis of the risk difference from each stratum using Cochran Mantel-Haenszel weights. The analysis was stratified by randomisation protocol and HIV and CD4 cell count status.

[d] Patients were classified by the first event that made the patient unfavourable. Of the patients with an unfavourable outcome at Week 76 in the control arm, 29 patients had a treatment modification from their allocated treatment that included SIRTURO as part of a salvage regimen.

[e] Week 132 outcome reflects efficacy follow up until the last patient reached Week 96.

In Arm D, a favourable outcome at Week 76 was reported for 122/134 (91.0%) patients and sustained up to Week 132 in 116/134 (86.6%) patients.

The frequency of deaths was similar across treatment arms through Week 132. In the 40-week SIRTURO arm, 11/211 (5.2%) patients died; the most common cause of death was related to TB (5 patients). In the 40-week active control arm, 8/202 (4.0%) patients died, including 4 of 29 patients who received SIRTURO as part of a salvage treatment; the most common cause of death was related to respiratory pathology. The adjusted difference in proportion of fatal AEs between the 40-week SIRTURO arm and the 40-week active control arm was 1.2% [95% CI (-2.8%; 5.2%)]. In the 28-week SIRTURO arm, 2/143 (1.4%) patients died; one of the two deaths was also related to TB.

## Paediatric patients (12 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 Phase 2 trial that was designed to enrol 15 adolescent patients 12 years to less than 18 years of age with confirmed or probable pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid who were to complete at least 24 weeks of treatment. 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 to 17), weighed 38 kg to 75 kg, and were 80% female, 53% Black, 33% White and 13 % Asian.

In the subset of patients with MGIT culture positive pulmonary TB at baseline, treatment with SIRTURO resulted in conversion to a negative culture in 87.5% (7/8 MGIT culture evaluable patients) at Week 24, which was sustained at Week 120.

## 5.2 Pharmacokinetic properties

The pharmacokinetic parameters of bedaquiline and the M2 metabolite in adult patients at the recommended dosing regimen of SIRTURO (400 mg for 2 weeks followed by 200 mg three times per week) with food in the Phase 3 trial, STREAM Stage 2, are provided in Table 6.

**Table 6: Pharmacokinetic Parameters of Bedaquiline and M2 Following Repeated Dose Administration of SIRTURO in Adult Patients in STREAM Stage 2**

| **Parameter** | **Mean (SD)** | |
|---|---|---|
| | **Bedaquiline** | **M2** |
| **Week 2** | **(N=281)** | **(N=281)** |
| $C_{max}$ (ng/mL) | 3060 (1124) | 326 (135) |
| $AUC_{24h}$, ng.h/mL | 41510 (15064) | 7267 (3029) |
| **Week 24** | **(N=255)** | **(N=255)** |
| $C_{max}$ (ng/mL) | 1838 (684) | 233.9 (85) |
| $AUC_{168h}$, ng.h/mL | 163924 (65498) | 37255.1 (13998) |
| **Week 40** | **(N=144)** | **(N=144)** |
| $C_{max}$ (ng/mL) | 1787 (666) | 245.6 (103) |
| $AUC_{168h}$, ng.h/mL | 168376 (74476) | 39540.3 (17220) |

SD=Standard Deviation

### 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 700 mg single-dose and once daily 400 mg for 14 days. 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 humans. In animal studies, bedaquiline and its active N-monodesmethyl metabolite (M2) were extensively distributed to most tissues, however, brain uptake was low.

### Metabolism

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

### Elimination

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

### Pharmacokinetic/pharmacodynamic relationship

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

## Special populations

***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 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 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.

***Elderly (65 years of age and older)***

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

In five patients 65 to 69 years of age, the systemic bedaquiline exposure was similar to that of other adults.

***Renal impairment***

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

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

***Hepatic impairment***

After single-dose administration of SIRTURO to 8 patients with moderate hepatic impairment (Child Pugh B), exposure to bedaquiline and M2 ($AUC_{672h}$) was 19% lower compared to healthy patients. No dose adjustment is deemed necessary in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population (see **section 4.2 Dose and method of administration**).

## Other Populations

***Race***

In a population pharmacokinetic analysis of TB patients treated with SIRTURO, exposure to bedaquiline was found to be lower in Black patients than in patients from other race categories. This lower bedaquiline exposure in Black patients was not associated with lower efficacy in clinical trials, and no dose adjustment is needed.

***Gender***

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

***HIV Co-infection***

Bedaquiline exposure in patients coinfected with HIV was similar to that in patients not coinfected with HIV.

## 5.3 Preclinical safety data

### Carcinogenicity

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

### Genotoxicity

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

### Fertility

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

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Colloidal anhydrous silica

Maize starch

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Polysorbate 20

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

SIRTURO has a shelf-life of 3 years.

## 6.4 Special precautions for storage

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

Keep out of the sight and reach of children.

## 6.5 Nature and contents of container

SIRTURO is supplied as:

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

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

## 6.6 Special precautions for disposal

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

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland
NEW ZEALAND
Telephone: 0800 800 806
Email: medinfo@janau.jnj.com

## 9. DATE OF FIRST APPROVAL

18 August 2016

## 10. DATE OF REVISION OF THE TEXT

04 August 2025

## Summary table of changes

| Section | Summary of new information |
|---|---|
| 4.8 | Updated section with STREAM stage 2 safety data |
| 5.1 | Minor statistical correction adult Study C208 clinical studies data. |