1. NAME OF THE MEDICINAL PRODUCT

SIRTURO

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

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 for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Treatment with SIRTURO should be initiated and monitored by a physician experienced in the management of multi-drug resistant *Mycobacterium tuberculosis*.

SIRTURO should be used in combination with at least three medicinal products 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 four medicinal products to which the patient's isolate is likely to be susceptible. Consideration should be given to WHO guidelines when selecting the appropriate combination regimen. Treatment with the other agents in the regimen should continue after completion of treatment with SIRTURO. Refer to the Summary of Product Characteristics of the medicinal products used in combination with SIRTURO for their specific dosing recommendations.

It is recommended that SIRTURO is administered by directly observed therapy (DOT).

Posology

The recommended dosage is:
- Weeks 1-2: 400 mg (4 tablets of 100 mg) **once daily**
- Weeks 3-24: 200 mg (2 tablets of 100 mg) **three times per week** (with at least 48 hours between doses).

Treatment duration
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).

Missed doses
Patients should be advised to take SIRTURO exactly as prescribed and to complete the full course of therapy.

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

If a dose is missed from week three onwards, patients should take the missed dose of 200 mg as soon as possible and then resume the three times a week regimen.

Elderly population (≥ 65 years of age)
There is limited clinical data (n = 2) on the use of SIRTURO in elderly patients.

Hepatic impairment
No dose adjustment is necessary for SIRTURO in patients with mild or moderate hepatic impairment (see section 5.2). SIRTURO should be used with caution in patients with moderate hepatic impairment (see section 5.2). SIRTURO has not been studied in patients with severe hepatic impairment and is not recommended in this population.

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis, SIRTURO should be used with caution (see section 5.2).

Paediatric population
The safety and efficacy of SIRTURO in children aged < 18 years have not yet been established.
No data are available.

Method of administration

SIRTURO should be taken orally with food, as administration with food increases oral bioavailability by about 2-fold (see section 5.2). SIRTURO tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There are no clinical data on the use of SIRTURO to treat:
- extra-pulmonary tuberculosis (e.g. central nervous system, bone)
- infections due to mycobacterial species other than *Mycobacterium tuberculosis*
- latent infection with *Mycobacterium tuberculosis*

There are no clinical data on the use of SIRTURO as part of combination regimens used to treat drug-susceptible *Mycobacterium tuberculosis*.

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 prevent 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 5.1). The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with SIRTURO treatment. For additional information on deaths in the C209 trial, see section 5.1.

Cardiovascular safety

Bedaquiline prolongs the QTc interval. An electrocardiogram should be obtained before initiation of treatment and at least monthly after starting treatment with bedaquiline. 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 4.5 and 4.8).

When bedaquiline is co-administered with other medicinal products that prolong the QTc interval (including delamanid and levofloxacin), an additive or synergistic effect on QT prolongation cannot be excluded (see section 4.5). Caution is recommended when prescribing bedaquiline concomitantly with medicinal products with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring, including frequent electrocardiogram assessment, is recommended.

In the event that co-administration of clofazimine with bedaquiline is necessary, clinical monitoring, including frequent electrocardiogram assessment, is recommended (see section 4.5).

SIRTURO treatment initiation is not recommended in patients with the following, unless the benefits of bedaquiline are considered to outweigh the potential risks:

- Heart failure;
- QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram);
- 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;
- Concomitant administration of fluoroquinolone antibiotics that have a potential for significant QT prolongation (i.e., gatifloxacin, moxifloxacin and sparfloxacin).
- Hypokalemia

SIRTURO treatment must be discontinued if the patient develops:

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

If syncope occurs, an electrocardiogram should be obtained to detect any QT prolongation.

Hepatic safety

Increases in transaminases or aminotransferase elevations accompanied by total bilirubin ≥ 2x ULN were seen in clinical trials during administration of SIRTURO with the background regimen (see section 4.8). Patients should be monitored throughout the treatment course, since the increases in liver enzymes were slow to appear and increased gradually during the 24 weeks. Monitor symptoms and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline, monthly while on treatment, and as needed. 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 medicinal product should be discontinued.
Other hepatotoxic medicinal products and alcohol should be avoided while on SIRTURO, especially in patients with diminished hepatic reserve.

Interactions with other medicinal products

CYP3A4 inducers
Bedaquiline is metabolised by CYP3A4. Co-administration of bedaquiline and medicinal products that induce CYP3A4 may decrease bedaquiline plasma concentrations and reduce its therapeutic effect. Co-administration of bedaquiline and moderate or strong CYP3A4 inducers used systemically should, therefore, be avoided (see section 4.5).

CYP3A4 inhibitors
Co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions (see section 4.5). Therefore, the combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided. If co-administration is required, more frequent electrocardiogram monitoring and monitoring of transaminases is recommended.

Patients infected with human immunodeficiency virus (HIV)

There are no clinical data on the safety and efficacy of bedaquiline when co-administered with antiretroviral agents.

There are only limited clinical data on the efficacy of bedaquiline in HIV-infected patients not receiving antiretroviral (ARV) therapy. Those patients studied all had CD4+ cell counts greater than 250 x 10^6 cells/l (N = 22; see section 4.5).

Lactose intolerance and lactase deficiency

SIRTURO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The elimination of bedaquiline has not been fully characterised *in vivo*. CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2). Urinary excretion of bedaquiline is negligible. Bedaquiline and M2 are not substrates or inhibitors of P-glycoprotein.

CYP3A4 inducers

Bedaquiline exposure may be reduced during co-administration with inducers of CYP3A4.

In an interaction study of single-dose bedaquiline and once daily rifampicin (strong inducer) in healthy subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)]. Due to the possibility of a reduction of the therapeutic effect of bedaquiline due to a decrease in systemic exposure, co-administration of bedaquiline and moderate or strong CYP3A4 inducers (e.g. efavirenz, etravirine, rifamycins including rifampicin, rifapentine and rifabutin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*)) used systemically should be avoided.

CYP3A4 inhibitors

Bedaquiline exposure may be increased during co-administration with inhibitors of CYP3A4.

The short-term co-administration of bedaquiline and ketoconazole (potent CYP3A4 inhibitor) in healthy subjects increased the exposure (AUC) to bedaquiline by 22% [90% CI (12; 32)]. A more pronounced effect on bedaquiline may be observed during prolonged co-administration of ketoconazole or other inhibitors of CYP3A4.

There are no safety data from bedaquiline multiple dose trials which utilised a dose higher than the indicated dose. Due to the potential risk of adverse reactions due to an increase in systemic exposure, prolonged co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors (e.g. ciprofloxacin, erythromycin, fluconazole, clarithromycin, ketoconazole, ritonavir) used systemically for more than 14 consecutive days should be avoided. If co-administration is required, more frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4).

Other antituberculosis medicinal products

The short-term co-administration of bedaquiline with isoniazid/pyrazinamide in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with bedaquiline.
In a placebo-controlled clinical study in patients with multi-drug resistant *Mycobacterium tuberculosis*, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

Antiretroviral medicinal products

In an interaction study of single-dose bedaquiline and multiple-dose lopinavir/ritonavir, exposure (AUC) to bedaquiline was increased by 22% [90% CI (11; 34)]. A more pronounced effect on bedaquiline plasma exposures may be observed during prolonged co-administration with lopinavir/ritonavir. Published data on patients treated with bedaquiline as part of therapy for drug-resistant TB and lopinavir/ritonavir-based ART have shown that bedaquiline exposure (AUC) over 48 hours was increased approximately 2 fold. This increase is likely due to ritonavir. If the benefit outweighs the risk, SIRTURO may be used with caution when co-administered with lopinavir/ritonavir. Increases in plasma exposure to bedaquiline would be expected when it is co-administered with other ritonavir-boosted HIV protease inhibitors. Of note, no change in bedaquiline dosing is recommended in case of co-treatment with lopinavir/ritonavir or other ritonavir-boosted HIV protease inhibitors. There are no data to support a lowered bedaquiline dose in such circumstances.

Co-administration of single-dose bedaquiline and multiple-dose nevirapine did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on co-administration of bedaquiline and antiretroviral agents in patients co-infected with human immunodeficiency virus and multi-drug

resistant *Mycobacterium tuberculosis* are not available (see section 4.4). Efavirenz is a moderate inducer of CYP3A4 activity and co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity, and is, therefore, not recommended.

QT interval prolonging medicinal products

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

QT interval and concomitant clofazimine use

In an open label Phase IIb trial, mean increases in QTcF were larger in the 17 subjects who were using concomitant clofazimine at week 24 (mean change from reference of 31.9 ms) than in subjects who were not using concomitant clofazimine at week 24 (mean change from reference of 12.3 ms) (see section 4.4).

Paediatric population

Sirturo is not indicated for use in paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of SIRTURO in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure**,** avoid the use of SIRTURO during pregnancy unless the benefit of therapy is considered to outweigh the risks.

Breastfeeding

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

In rats, concentrations of bedaquiline in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma. Body weight decreases in pups were noted in high dose groups during the lactation period (see section 5.3).

Because of the potential for adverse reactions in breastfed infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from SIRTURO therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Fertility

No human data on the effect of bedaquiline on fertility are available. In female rats, there was no effect on mating or fertility with bedaquiline treatment, however some effects were observed in male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Bedaquiline may have a minor influence on the ability to drive and use machines. Dizziness has been reported in some patients taking bedaquiline and should be considered when assessing a patient’s ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Adverse drug reactions for SIRTURO were identified from pooled Phase IIb clinical trial data (both controlled and uncontrolled C208 and C209) containing 335 patients who received SIRTURO in combination with a background regimen of tuberculosis medicinal products. The basis of assessment of causality between the adverse drug reactions 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 adverse drug reactions (> 10.0% of patients) during treatment with SIRTURO in the controlled trials were nausea (35.3% in the SIRTURO group vs 25.7% in the placebo group), arthralgia (29.4% vs 20.0%), headache (23.5% vs 11.4%), vomiting (20.6% vs 22.9%) and dizziness (12.7% vs 11.4%). Refer to the Summary of Product Characteristics of the medicinal products 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 the table below.
Adverse drug reactions are listed by system organ class (SOC) and frequency. Frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

System Organ Class (SOC)	Frequency Category	ADRs
Nervous system disorders	Very Common	Headache, dizziness
Cardiac disorders	Common	Electrocardiogram QT prolonged
Gastrointestinal disorders	Very Common	Nausea, vomiting
	Common	Diarrhoea
Hepatobiliary disorders	Common	Transaminases increased*
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia
	Common	Myalgia

* Terms represented by 'transaminases increased' included AST increased, ALT increased, hepatic enzyme increased, hepatic function abnormal, and transaminases increased (see section below).

Description of selected adverse reactions

Cardiovascular
In the controlled Phase IIb study (C208), mean increases from baseline values 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 from baseline values 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 from baseline values in QTcF in the placebo group during the first 24 weeks was 6.2 ms (also at week 18) (see section 4.4).
In the Phase IIb, open label study (C209), where patients with no treatment options received other QT-prolonging medicinal products used to treat tuberculosis, including clofazimine, concurrent use with SIRTURO resulted in additive QT prolongation, proportional to the number of QT prolonging medicinal products in the treatment regimen.
Patients receiving SIRTURO alone with no other QT prolonging medicinal product developed a maximal mean QTcF increase over baseline of 23.7 ms with no QT duration in excess of 480 ms, whereas patients with at least 2 other QT prolonging medicinal products developed a maximal mean QTcF prolongation of 30.7 ms over baseline, resulting in a QTcF duration in excess of 500 ms in one patient.

There were no documented cases of Torsade de Pointes in the safety database (see section 4.4). See section 4.5, QT interval and concomitant clofazimine use, for further information regarding patients using clofazimine concomitantly.

Increased transaminases
In study C208 (stage 1 and 2), aminotransferase elevations of at least 3 x ULN developed more frequently in the SIRTURO treatment group (11/102 [10.8%] versus 6/105 [5.7%]) in the placebo treatment group. In the SIRTURO treatment group, the majority of these increases occurred throughout the 24 weeks of treatment and were reversible. During the investigational phase in stage 2 of study C208, increased aminotransferases were reported in 7/79 (8.9%) patients in the SIRTURO treatment group compared to 1/81 (1.2%) in the placebo treatment group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

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

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 electrocardiogram (QT interval) monitoring should be taken in case of deliberate or accidental overdose. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma. Clinical monitoring should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Bedaquiline is a diarylquinoline. Bedaquiline specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an essential enzyme 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 has activity against *Mycobacterium tuberculosis* with a minimal inhibitory concentration (MIC) for drug-sensitive as well as drug-resistant strains (multi-drug resistant including pre-extensively drug resistant strains, extensively drug resistant strains) in the range of ≤ 0.008-0.12 mg/l. The *N*-monodesmethyl metabolite (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.

Bedaquiline is bacteriostatic for many non-tuberculous mycobacterial species. *Mycobacterium xenopi*, *Mycobacterium novocastrense*, *Mycobacterium shimoidei* and non-mycobacterial species are considered inherently resistant to bedaquiline.

Pharmacokinetic/pharmacodynamic relationship

Within the concentration range achieved with the therapeutic dose, no pharmacokinetic/pharmacodynamic relationship was observed in patients.

Mechanisms of resistance

Acquired resistance mechanisms that affect bedaquiline MICs include mutations in the *atpE* gene, which codes for the ATP synthase target, and in the *Rv0678* gene, which regulates 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 mg/l. 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 mg/l. The majority of isolates that are phenotypically resistant to bedaquiline are cross-resistant to clofazimine. Isolates that are resistant to clofazimine can still be susceptible to bedaquiline.

The impact of high baseline bedaquiline MICs, the presence of *Rv0678* based mutations at baseline, and/or increased post-baseline bedaquiline MICs on microbiologic outcomes is unclear because of the low incidence of such cases in the Phase II trials.

Susceptibility testing breakpoints

When available, the clinical microbiology laboratory should provide the physician with the results of *in vitro* susceptibility test results for antimicrobial medicinal products used in resident hospitals as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting a combination of antibacterial medicinal products for treatment.

Breakpoints

Minimal inhibitory concentration (MIC) breakpoints are as follows:

Epidemiological Cut-Off (ECOFF)	0.25 mg/l
Clinical Breakpoints	S ≤ 0.25 mg/l; R > 0.25 mg/l

S = susceptible
R = resistant

Commonly susceptible species
Mycobacterium tuberculosis

Inherently resistant organisms
Mycobacterium xenopi
Mycobacterium novocastrense
Mycobacterium shimoidei
Non-mycobacterial species

Clinical efficacy and safety

The following definitions apply for resistance categories used:

Multi-drug resistant *Mycobacterium tuberculosis* ($MDR_{H\&R}$-TB): isolate resistant to at least isoniazid and rifampicin, but susceptible to fluoroquinolones and second line injectable agents.
Pre-extensively drug resistant tuberculosis (pre-XDR-TB): isolate resistant to isoniazid, rifampicin, and *either* any fluoroquinolone *or* at least one second line injectable agent (but not to both a fluoroquinolone and a second line injectable agent).
Extensively drug resistant tuberculosis (XDR-TB): isolate resistant to isoniazid, rifampicin, any fluoroquinolone, and at least one second line injectable agent.

A Phase IIb, placebo-controlled, double-blind, randomised trial (C208) evaluated the antibacterial activity, safety, and tolerability of SIRTURO in newly diagnosed patients with sputum smear-positive pulmonary $MDR_{H\&R}$- and pre-XDR-TB. Patients received SIRTURO (n = 79) or placebo (n = 81) for 24 weeks, both in combination with a preferred 5-drug background regimen (BR) consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone. After the 24-week investigational period, the background regimen was continued to complete 18 to 24 months of total multi-drug resistant *Mycobacterium tuberculosis* treatment. A final evaluation was conducted at Week 120. Main demographics were as follows: 63.1% were males, median age 34 years, 35% were Black, and 15% were HIV positive. Cavitation in one lung was seen in 58% of patients, and in both lungs in 16%. For patients with full characterisation of resistance status, 76% (84/111) were infected with an $MDR_{H\&R}$-TB strain and 24% (27/111) with a pre-XDR-TB strain.

SIRTURO was administered as 400 mg once daily for the first 2 weeks, and as 200 mg 3 times/week for the following 22 weeks.

The primary outcome parameter was the time to sputum culture conversion (i.e. the interval between the first SIRTURO intake and the first of two consecutive negative liquid cultures from sputum collected at least 25 days apart) during treatment with SIRTURO or placebo (median time to conversion was 83 days for the SIRTURO group, 125 days for the placebo group (hazard ratio, 95% CI: 2.44 [1.57; 3.80]), $p < 0.0001$).

In the SIRTURO group, no or only minor differences in time to culture conversion and culture conversion rates were observed between patients with pre-XDR-TB and patients with $MDR_{H\&R}$-TB.

Response rates at week 24 and week 120 (i.e. around 6 months after stopping all therapy) are presented in table 1.

Table 1: Culture conversion Status

Culture Conversion Status, n (%)	mITT population			
	N	SIRTURO/BR	N	Placebo/BR
Overall responder at Week 24	66	52 (78.8%)	66	38 (57.6%)
Patients with $MDR_{H\&R}$-TB	39	32 (82.1%)	45	28 (62.2%)
Patients infected with a pre-XDR-TB	15	11 (73.3%)	12	4 (33.3%)
Overall non-responder* at Week 24	66	14 (21.2%)	66	28 (42.4%)
Overall responder at Week 120	66	41 (62.1%)	66	29 (43.9%)
Patients with $MDR_{H\&R}$-TB	39[#]	27 (69.2%)	46[# §]	20 (43.5%)

Patients infected with pre-XDR-TB	15[#]	9 (60.0%)	12[#]	5 (41.7%)
Overall non-responder* at Week 120	66	25 (37.9%)	66	37 (56.1%)
Failure to convert	66	*8 (12.1%)*	66	*15 (22.7%)*
Relapse[†]	66	*6 (9.1%)*	66	*10 (15.2%)*
Discontinued but converted	66	*11 (16.7%)*	66	*12 (18.2%)*

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

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

Extent of resistance based on central laboratory drug susceptibility testing results was not available for 20 subjects in the mITT population (12 in the SIRTURO group and 8 in the placebo group). These subjects were excluded from the subgroup analysis by extent of resistance of *M tuberculosis* strain.

§ Central laboratory drug susceptibility testing results became available for one additional placebo subject after the week 24 interim analysis.

Study C209 evaluated the safety, tolerability, and efficacy of 24 weeks treatment with open-label SIRTURO as part of an individualized 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 ($MDR_{H\&R}$-, 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 $MDR_{H\&R}$-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 drug 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, sputum culture conversion was seen in 148/205 (72.2%) patients. Conversion rates at week 120 were highest (73.1%; 68/93) in patients with $MDR_{H\&R}$-TB, 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 substances (*in vitro*) in their background regimen.

Of the 163 patients who were responders at week 24, 139 patients (85.3%) were still responders at week 120. Twenty-four of these 24-week responders (14.7%) were considered non-responders at week 120, of which 19 patients had prematurely discontinued the trial while being culture converted and 5 patients had experienced relapse. Of the 42 patients who were non-responders at week 24, confirmed culture conversion after week 24 (i.e., after bedaquiline dosing ended but the background regimen was continued) occurred in 9 patients (21.4%) and was maintained at week 120.

Mortality

In the randomised Phase IIb study (C208, stage 2) a higher rate of deaths was seen in the SIRTURO treatment group (12.7%; 10/79 patients) compared to the placebo treatment group (3.7%; 3/81 patients). 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 patients 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 Phase IIb, open label study (C209), 6.9% (16/233) patients died. The most common cause of death as reported by the investigator was tuberculosis (9 patients). All but one patients who died of tuberculosis had not converted or had relapsed. The causes of death in the remaining patients varied.

Paediatric population

Sirturo is not indicated for use in paediatric population.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of bedaquiline have been evaluated in adult healthy subjects and in adult multi-drug resistant tuberculosis-infected patients. Exposure to bedaquiline was lower in multi-drug resistant tuberculosis-infected patients than in healthy subjects.

Absorption

Maximum plasma concentrations (C_{max}) are typically achieved at about 5 hours post-dose. C_{max} and the area under the plasma concentration-time curve (AUC) increased proportionally up to the highest doses studied (700 mg single-dose and once daily 400 mg multiple doses). Administration of bedaquiline with food increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. Therefore, bedaquiline should be taken with food to enhance its oral bioavailability.

Distribution

The plasma protein binding of bedaquiline is > 99.9% in all species tested, including human. The plasma protein binding of the *N*-monodesmethyl metabolite (M2) in humans is at least 99.8%. In animals, bedaquiline and its active *N*-monodesmethyl metabolite (M2) are extensively distributed to most tissues, however, brain uptake was 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).

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 or CYP2C19 activities.

Bedaquiline and M2 were not substrates of P-gp *in vitro*. Bedaquiline was a weak OCT1, OATP1B1 and OATP1B3 substrate *in vitro*, while M2 was not. Bedaquiline was not a substrate of MRP2 and BCRP *in vitro*. Bedaquiline and M2 did not inhibit the transporters P-gp, OATP1B1, OATP1B3, BCRP, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2 at clinically relevant concentrations *in vitro*. An in vitro study indicated a potential for bedaquiline to inhibit BCRP at the concentrations achieved in the intestine after oral administration. The clinical relevance is unknown.

Elimination

Based on the preclinical studies, the bulk of the administered dose is eliminated in faeces. The urinary excretion of unchanged bedaquiline was < 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged active substance is insignificant. After reaching C_{max}, bedaquiline

concentrations decline tri-exponentially. The mean terminal elimination half-life of both bedaquiline and the active *N*-monodesmethyl metabolite (M2) is about 5 months (ranging from 2 to 8 months). This long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.

Special populations

Hepatic impairment
A single-dose study of SIRTURO in 8 subjects with moderate hepatic impairment (Child-Pugh B) demonstrated exposure to bedaquiline and M2 (AUC_{672h}) was 19% lower compared to healthy subjects. No dose adjustment is deemed necessary in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment (see section 4.2).

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 tuberculosis patients treated with SIRTURO 200 mg three times a week, creatinine clearance (range: 40 to 227 ml/min) 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. However, in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis, bedaquiline concentrations may be increased due to alteration of active substance 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
Sirturo is not indicated for use in paediatric population.

Elderly patients
There is limited clinical data (n = 2) on the use of SIRTURO in tuberculosis patients aged 65 years and older.

In a population pharmacokinetic analysis of tuberculosis patients (age range 18 years to 68 years) treated with SIRTURO age was not found to influence the pharmacokinetics of bedaquiline.

Race
In a population pharmacokinetic analysis of tuberculosis patients treated with SIRTURO, exposure to bedaquiline was found to be lower in Black patients than in patients from other race categories. This low exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials. Furthermore, response rates in patients that completed the bedaquiline treatment period were comparable between different race categories in the clinical trials.

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

5.3 Preclinical safety data

Animal toxicology studies have been conducted with bedaquiline administration up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. The plasma bedaquiline exposure (AUC) in rats and dogs was similar to that observed in humans. Bedaquiline was associated with effects in target organs which included monocytic phagocytic system (MPS), skeletal muscle, liver, stomach, pancreas and heart muscle. All of these toxicities except effects on MPS were monitored clinically. In the MPS

of all species, pigment-laden and/or foamy macrophages were also seen in various tissues, consistent with phospholipidosis. The significance of phospholipidosis in humans is unknown. Most of the observed changes occurred after prolonged daily dosing and subsequent increases in plasma and tissue concentrations of the active substance. After treatment cessation, all indications of toxicity exhibited at least partial recovery to good recovery.

In a rat carcinogenicity study, bedaquiline, at the high doses of 20 mg/kg/day in males and 10 mg/kg/day in females, did not induce any treatment-related increases in tumour incidences. Compared to the exposures (AUC) observed in subjects with MDR-TB in the bedaquiline Phase II trials, the exposures (AUC) in rats at high doses were similar in males and 2-fold higher in females for bedaquiline, and 3-fold higher in males and 2-fold higher in females for M2.

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

Bedaquiline had no effects on fertility when evaluated in female rats. Three of 24 male rats treated with high bedaquiline doses failed to produce offspring in the fertility study. Normal spermatogenesis and a normal amount of spermatozoa in the epidydimides were noted in these animals. No structural abnormalities in the testes and epididymides were seen after up to 6-months of bedaquiline treatment. No relevant bedaquiline-related effects on developmental toxicity parameters were observed in rats and rabbits. The corresponding plasma exposure (AUC) was 2-fold higher in rats compared to humans. In the rat, no adverse effects were observed in a pre- and post-natal development study at maternal plasma exposure (AUC) similar to humans and exposure in the offspring 3-fold higher than in adult humans. There was no effect of maternal treatment with bedaquiline at any dose level on sexual maturation, behavioural development, mating performance, fertility or reproductive capacity of the F1 generation animals. Body weight decreases in pups were noted in high dose groups during the lactation period after exposure to bedaquiline via milk and were not a consequence of in utero exposure. Concentrations of bedaquiline in milk were 6- to12-fold higher that the maximum concentration observed in maternal plasma.
In a juvenile rat toxicity study, the no observed adverse effect level (NOAEL) was 15 mg/kg/day (maximum dose 45mg/kg/day) for observations of diffuse inflammation and/or degeneration in skeletal muscle (reversible), oesophagus (reversible) and tongue (reversible), liver hypertrophy (reversible) and corticomedullary renal mineralization (partial recovery in males, and no recovery in females within 8 weeks after end of exposure). The NOAEL corresponds to a plasma AUC24h of 13.1 and 35.6 mcg.h/mL for bedaquiline (~0.7x clinical dose) and 10.5 and 16.3 mcg.h/mL for the N-monodesmethyl metabolite of bedaquiline (M2) in males and females (~1.8x clinical dose), respectively.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that bedaquiline has the potential to be persistent, bioaccumulative and toxic to the environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Maize starch
Croscarmellose sodium
Hypromellose
Magnesium stearate
Silica, colloidal anhydrous
Polysorbate 20

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening can be used 24 weeks and no later than the expiry date of the product.

6.4 Special precautions for storage

No special storage requirements. It is recommended to store this medicinal product at room temperature.

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

6.5 Nature and contents of container

White HDPE bottle with child-resistant polypropylene (PP) closure with aluminium induction seal liner containing 188 tablets.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused product or waste material should be disposed of in accordance with local requirements (see section 5.3).

7. MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel

8. MANUFACTURER

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

Revised in June 2022 according to MoH guidleines.