ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SIRTURO 20 mg tablets
SIRTURO 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SIRTURO 20 mg tablets
Each tablet contains bedaquiline fumarate equivalent to 20 mg of bedaquiline.

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

Excipient with known effect

Each 100 mg tablet contains 145 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SIRTURO 20 mg tablets
Tablet.

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

The tablet can be divided into equal doses.

SIRTURO 100 mg tablets
Tablet.

Uncoated, white to almost white round biconvex tablet, 11 mm in diameter, with debossing of "T" over "207" on one side and "100" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SIRTURO is indicated for use as part of an appropriate combination regimen in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid.
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 TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid.
Consideration should be given to WHO guidelines when selecting the appropriate combination regimen.

Only use SIRTURO in combination with other medicinal products to which the patient’s isolate has been shown to be susceptible *in vitro* or is likely to be susceptible. 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

Adult Patients

The recommended dosage for SIRTURO in adult (18 years and older) patients is shown in Table 1.

Table 1: Recommended Dosage of SIRTURO in Adult Patients

Population	**Dosing Recommendation**	
	Weeks 1 to 2	**Weeks 3 to 24**
Adults (18 years and older)	400 mg orally **once daily**	200 mg orally **three times per week** [a]

[a] At least 48 hours between doses

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

Paediatric Patients

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

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

Body Weight	**Dosage Recommendation**	
	Weeks 1 to 2	**Weeks 3 to 24**
Greater than or equal to 15 kg to less than 20 kg	160 mg orally **once daily**	80 mg orally **three times per week** [a]
Greater than or equal to 20 kg to less than 30 kg	200 mg orally **once daily**	100 mg orally **three times per week** [a]
Greater than or equal to 30 kg	400 mg orally **once daily**	200 mg orally **three times per week** [a]

[a] At least 48 hours between doses

The total duration of treatment with SIRTURO is 24 weeks. SIRTURO should be 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 sections 4.8 and 5.1).

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 as soon as possible and then resume the three times a week regimen. The total dose of SIRTURO during a 7-day period should not exceed the recommended weekly dose (with at least 24 hours between each intake).

Elderly population
There are limited clinical data on the use of SIRTURO in elderly patients (see section 5.2).

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 less than 5 years of age or weighing less than 15 kg have not yet been established. No data are available.

SIRTURO may be included in the treatment regimen for children greater than or equal to 5 years of age and weighing at least 15 kg with confirmed or probable pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid that is diagnosed based on clinical signs and symptoms of pulmonary TB, appropriate epidemiological context, and in line with international/local guidelines (see section 4.1).

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

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

SIRTURO 20 mg tablets
*Administration of 20 mg Tablets to Patients Who **Can** Swallow Intact Tablets:*
SIRTURO 20 mg tablet should be swallowed whole, or in two equal halves divided along the functional score line, with water and taken with food.

*Administration of 20 mg Tablets to Patients Who **Cannot** Swallow Intact Tablets:*
Dispersed in Water and Administered with Beverage or Soft Food
For patients who have difficulty swallowing intact tablets, SIRTURO 20 mg tablet can be dispersed in water and administered. To aid with administration, the dispersed mixture in water can be further mixed with a beverage (e.g., water, milk product, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g., yoghurt, apple sauce, mashed banana or porridge) as follows:

- Disperse tablets in water (maximum of 5 tablets in 5 mL of water) in a drinking cup.
- Mix the contents of the cup well until the tablets are completely dispersed and then orally administer the contents of the cup immediately with food. To aid with oral administration, the dispersed mixture in water can be further mixed with at least 5 mL of beverage or 1 teaspoonful of soft food and then orally administer the contents of the cup immediately.
- If the total dose requires more than 5 tablets, repeat the above preparation steps with the appropriate number of additional tablets until the desired dose is reached.

- Ensure no tablet residue is left in the cup, rinse with beverage or add more soft food and orally administer the contents of the cup immediately.

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

Refer to section 6.6 for information on administration through a feeding tube.

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 TB (e.g., central nervous system, bone)
- infections due to mycobacterial species other than *M. tuberculosis*
- latent infection with *M. tuberculosis*

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

Resistance to bedaquiline

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

QT prolongation

SIRTURO may prolong the QT interval. An electrocardiogram should be obtained before initiation of treatment with SIRTURO and at least monthly after starting treatment to monitor the QTc interval. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected (see sections 4.5 and 4.8).

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
- Hypokalaemia

When bedaquiline is co-administered with other medicinal products that prolong the QTc interval (including clofazimine, delamanid, or fluoroquinolones), an additive effect on QT prolongation is expected (see section 4.5). Treatment with SIRTURO may be considered after a favourable benefit-risk assessment and with ECG monitoring.

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 accompanied by total bilirubin ≥2x ULN were seen in clinical trials in adult and paediatric patients during administration of SIRTURO with the background regimen (see section 4.8). Patients should be monitored 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.

Paediatric patients

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

Interactions with other medicinal products

CYP3A4 inducers
Bedaquiline is metabolised by CYP3A4. Co-administration of SIRTURO with moderate or strong CYP3A4 inducers decreases bedaquiline plasma concentrations and may reduce the therapeutic effect of SIRTURO. Co-administration of SIRTURO and moderate or strong CYP3A4 inducers used systemically, such as efavirenz and rifamycins (i.e., rifampicin, rifapentine and rifabutin) should, therefore, be avoided (see section 4.5).

Lactose intolerance and lactase deficiency

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

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

In an interaction study of single-dose bedaquiline and once daily rifampicin (strong inducer) in healthy adults, the 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 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.

In the Phase III study, co-administration of the weak CYP3A4 inducer nevirapine and SIRTURO as part of combination therapy for up to 40 weeks in patients co-infected with HIV resulted in a mild decrease in average bedaquiline exposure (AUC) compared to a subgroup without HIV co-infection. This exposure difference was however not associated with a 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 co-administration of SIRTURO and CYP3A4 inhibitors is allowed, and no dose adjustment is needed.

The short-term co-administration of bedaquiline and ketoconazole (strong CYP3A4 inhibitor) in healthy adults increased the mean bedaquiline exposure (AUC) by 22% [90% CI (12; 32)]. In healthy adults, 10 days of co-administration of another strong CYP3A4 inhibitor, clarithromycin, with single-dose bedaquiline increased the mean bedaquiline exposure (AUC) by 14% [90% CI (9; 19)]. A more pronounced effect on bedaquiline may be observed during prolonged co-administration of CYP3A4 inhibitors.

In the Phase III trial, long-term co-administration of SIRTURO as part of a combination therapy and lopinavir/ritonavir in patients co-infected with HIV resulted in a mild increase in mean bedaquiline exposure at Week 24 compared to a subgroup without HIV co-infection. No dose adjustment is required.

In the open-label Phase IIb trial, long-term co-administration of clofazimine and SIRTURO, as part of a combination therapy for up to 24 weeks, did not affect bedaquiline exposure.

Other antituberculosis medicinal products

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 adults with TB, no major impact of co-administration of SIRTURO on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

QT interval prolonging medicinal products

In an open-label Phase IIb 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 III trial, additive increases in QTcF were observed when combining clofazimine and levofloxacin with SIRTURO (see sections 4.4 and 4.8).

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 sections 4.4 and 4.8).

Paediatric population

Interaction studies have only been performed in adults.

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.

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 mother had a high concentration of bedaquiline in breast milk, with a milk to plasma ratio of 14:1. This is consistent with data from animal studies (see section 5.3). Available information indicates that systemic exposure in breastfed infants may reach levels similar to those observed in the breastfeeding mothers treated with bedaquiline. The clinical consequence of this exposure is unknown. Women who are treated with bedaquiline should not breastfeed.

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 reactions for SIRTURO were identified from Phase IIb clinical trial data (both controlled and uncontrolled, C208 and C209) in 335 adult patients who received SIRTURO for 8 weeks or 24 weeks. No new adverse reactions were identified in the Phase III 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 open-label Phase III trial were QT prolongation (61% in the SIRTURO group vs 56% in the control group), nausea (54% vs 63%), vomiting (54% vs 62%), arthralgia (45% vs 33%), transaminases increased (30% vs 29%), dizziness (18% vs 21%) and headache (17% vs 18%). 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 reactions to SIRTURO based on reported safety data from Phase II and Phase III trials in adult patients treated with SIRTURO are presented in the Table below.

Adverse 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[a]	ARs
Nervous system disorders	Very Common	Headache, dizziness
Gastrointestinal disorders	Very Common	Nausea, vomiting
	Common	Diarrhoea
Hepatobiliary disorders	Very Common	Transaminases increased[b,c]
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia
	Common	Myalgia
Investigations	Very Common	Electrocardiogram QT prolonged[d]

[a] Frequencies derived from Phase III trial STREAM Stage 2 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] Terms represented by 'transaminases increased' included AST increased, ALT increased, hepatic enzyme increased, hepatic function abnormal, hypertransaminasaemia, and transaminases increased (see section below).

[c] Incidence of transaminases increased in the controlled Phase IIb study was Common (6.9% in the SIRTURO group and 1% in placebo control).

[d] Incidence of QT prolonged in Phase IIb study was Common (2.9% in the SIRTURO group and 3.8% in placebo control).

Description of selected adverse reactions

QT prolongation
Clinical trials of SIRTURO in adult TB patients collectively 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).

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 (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).

In the Phase IIb, open-label study (C209), where patients with no treatment options received other QT-prolonging medicinal products used to treat pulmonary TB including clofazimine, concurrent use with SIRTURO resulted in additive QT prolongation. In patients taking SIRTURO with no other QT-prolonging drugs, there were no patients with QTcF interval durations above 480 ms, and in patients who were taking at least two other QT-prolonging drugs, there was one patient with a QTcF interval duration above 500 ms.

In the controlled Phase III study, in which the 40-week SIRTURO and active control treatment groups 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 group 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 group 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 group compared to 7.4% in the non-SIRTURO-containing control group (see sections 4.4 and 4.5).

Increased transaminases
In Study C208 (Stage 1 and 2), transaminase elevations of at least 3 x ULN developed more frequently in the SIRTURO treatment group (11/101 [10.9%] versus 6/104 [5.8%]) 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 transaminases were reported in 7/78 (9.0%) patients in the SIRTURO treatment group compared to 1/80 (1.3%) in the placebo treatment group.

In the STREAM Stage 2 study, increased transaminases were reported in 63/211 (29.9%) patients in the 40-week SIRTURO treatment group versus 59/202 (29.2%) patients in the 40-week active control group.

Paediatric population

The safety assessment of bedaquiline is based on data from 30 paediatric patients greater than or equal to 5 years of age with confirmed or probable pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid (see section 5.1).

Overall, there was no indication of any differences in the safety profile in adolescents aged 14 years to less than 18 years (N=15) compared to that observed in the adult population.

In paediatric patients aged 5 years to less than 11 years (N=15), the most common adverse reactions were related to elevations in liver enzymes (5/15, 33%), reported as ALT/AST increased and hepatotoxicity; hepatotoxicity led to discontinuation of SIRTURO in three patients. Elevations in liver enzymes were reversible upon discontinuation of SIRTURO and background regimen. Among these 15 paediatric patients, no deaths occurred during treatment with SIRTURO.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Cases of intentional or accidental acute overdose with SIRTURO 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).

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 *M. tuberculosis*. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

Pharmacodynamic effects

Bedaquiline has activity against *M. tuberculosis* complex strains with a minimal inhibitory concentration (MIC) in the range of ≤0.008 to 0.25 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, Mycobacterium flavescens* 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 microbiological outcomes is unclear because of the low incidence of such cases in clinical trials.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for bedaquiline and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Commonly susceptible species
Mycobacterium tuberculosis

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

Clinical efficacy and safety

A Phase IIb, placebo-controlled, double-blind, randomised trial (C208) evaluated the antibacterial activity, safety, and tolerability of SIRTURO in newly diagnosed adult 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 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. 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 for the ITT population 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 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% (27/112) 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 between the first SIRTURO intake and the first of two consecutive negative MGIT 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 a *M. tuberculosis* strain resistant to rifampicin and isoniazid and patients with a *M. tuberculosis* strain also resistant to second-line injectables or fluoroquinolones.

Response rates at Week 24 and Week 120 (i.e., approximately 6 months after stopping all therapy) are presented in Table 3.

Table 3: Culture Conversion Status in C208

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 a *M. tuberculosis* strain resistant to rifampicin and isoniazid	39	32 (82.1%)	45	28 (62.2%)
Patients with a *M. tuberculosis* strain resistant to rifampicin and isoniazid, and also to second-line injectables or fluoroquinolones	15	11 (73.3%)	12	4 (33.3%)
Overall non-responder[a] 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 a *M. tuberculosis* strain resistant to rifampicin and isoniazid	39[b]	27 (69.2%)	46[b,c]	20 (43.5%)

Patients infected with a *M. tuberculosis* strain resistant to rifampicin and isoniazid, and also to second-line injectables or fluoroquinolones	15[b]	9 (60.0%)	12[b]	5 (41.7%)
Overall non-responder[a] at Week 120	66	25 (37.9%)	66	37 (56.1%)
Failure to convert	66	*8 (12.1%)*	66	*15 (22.7%)*
Relapse[d]	66	*6 (9.1%)*	66	*10 (15.2%)*
Discontinued but converted	66	*11 (16.7%)*	66	*12 (18.2%)*

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

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

[c] Central laboratory drug susceptibility testing results became available for one additional placebo patient after the Week 24 interim analysis.

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

During the trial, 12.7% (10/79) of the patients died in the SIRTURO treatment group (N=79) compared to 3.7% (3/81) of the 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.

Study C209 evaluated the safety, tolerability, and efficacy of 24 weeks treatment with open-label SIRTURO as part of an individualised treatment regimen in 233 adult patients who were sputum smear positive within 6 months prior to screening. This study included patients with *M. tuberculosis* strains of all three resistance categories (resistant to rifampicin and isoniazid, also resistant to second-line injectables or fluoroquinolones, and also resistant to second-line injectables and fluoroquinolones).

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 *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. Extent of resistance based on central laboratory drug susceptibility testing results was not available for 31 patients in the mITT population. These patients were excluded from the subgroup analysis by extent of resistance of *M. 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 *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 substances (*in vitro*) in their background regimen.

In the open-label C209 trial, 6.9% (16/233) of the 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 was a Phase III, open-label, multicentre, active-controlled, randomised trial conducted to evaluate the efficacy and safety of SIRTURO co-administered 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, with or without resistance additionally to isoniazid and/or second-line injectable agents or fluoroquinolones (but not both).

Patients were randomised to one of four treatment groups:

- Group A (N=32), the locally used treatment in accordance with 2011 WHO treatment guidelines with a recommended 20-month duration
- Group 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)
- Group 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)
- Group 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 Group C) or 26 weeks (in Group D). Changes in treatment regimen were permitted at the discretion of the investigator in all groups. Enrolment in Groups A and D was stopped prematurely due to changes in the standard of care for TB treatment.

The primary objective was to assess whether the proportion of patients with a favourable efficacy outcome in Group C was noninferior to that in Group B at Week 76.

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 encompassed clinically relevant 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 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), 12.5% of the patient's *M. tuberculosis* isolates were resistant 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.

Table 4 shows the proportion of patients with a favourable or unfavourable outcome at Week 76 in the STREAM Stage 2 Phase III trial. The proportion of participants with a favourable outcome at Week 76 was 82.7% in Group C compared to 71.1% in Group B. The main reason for an unfavourable outcome in both groups was extension or modification of the assigned treatment regimen. Limitations of the study included its open-label design; changes to the allocated treatment regimens were permitted in case of treatment failure, recurrence or serious toxicity.

Table 4: Primary Analysis in STREAM Stage 2 (Phase III Trial)

	mITT Population	
	SIRTURO[a] (N=196)	**Active Control[b] (N=187)**
Favourable outcome at Week 76 n (%)	162 (82.7)	133 (71.1)
Unfavourable outcome at Week 76 n (%)	34 (17.3)	54 (28.9)
Reasons for unfavourable outcome through Week 76[c]		
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)

mITT = modified intent-to-treat

[a] Group 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] Group 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] 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 group, 29 patients had a treatment modification from their allocated treatment that included SIRTURO as part of a salvage regimen.

The frequency of deaths was similar across treatment groups through Week 132. In the 40-week SIRTURO group, 11/211 (5.2%) patients died; the most common cause of death was related to TB (5 patients). In the 40-week active control group, 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 adverse events between the 40-week SIRTURO group and the 40-week active control group was 1.2% [95% CI (-2.8%; 5.2%)].

Paediatric population

The pharmacokinetics, safety and tolerability of SIRTURO in combination with a background regimen were evaluated in trial C211, a single-arm, open-label, multi-cohort Phase II trial in 30 patients with confirmed or probable pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid.

Paediatric patients (12 years to less than 18 years of age)
Fifteen patients had a median age of 16 years (range: 14 to 17 years), weighed 38 to 75 kg, and were 80% female, 53% Black, 33% White and 13% Asian. The patients were to complete at least 24 weeks of treatment with SIRTURO administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks using 100 mg tablets.

In the subset of patients with culture positive pulmonary TB at baseline, treatment with a regimen including bedaquiline resulted in conversion to a negative culture in 75.0% (6/8 microbiologically evaluable patients) at Week 24.

Paediatric patients (5 years to less than 12 years of age)
Fifteen patients had a median age of 7 years (range: 5 to 10 years), weighed 14 to 36 kg, and were 60% female, 60% Black, 33% White and 7% Asian. The patients were to complete at least 24 weeks of treatment with SIRTURO administered as 200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks using 20 mg tablets.

In the subset of patients with culture positive pulmonary TB at baseline, treatment with a regimen including bedaquiline resulted in conversion to a negative culture in 100% (3/3 microbiologically evaluable patients) at Week 24.

The European Medicines Agency has deferred the obligation to submit the results of studies with SIRTURO in one or more subsets of the paediatric population in the treatment of *M. tuberculosis* resistant to at least rifampicin and isoniazid (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of bedaquiline have been evaluated in healthy adults and in patients 5 years of age and older with active TB. Exposure to bedaquiline was lower in patients with pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid than in healthy adults.

In adult patients with pulmonary TB, following 2 weeks of 400 mg bedaquiline once daily, mean (SD) C_{max} and AUC_{24h}, ng·h/mL were 3060 (1124) ng/mL and 41510 (15064) ng·h/mL, respectively, for bedaquiline and 326 (135) ng/mL and 7267 (3029) ng·h/mL, respectively, for the M2 metabolite. Following 38 weeks of 200 mg bedaquiline three times weekly, mean (SD) C_{max} and AUC_{168h}, ng·h/mL were 1787 (666) ng/mL and 168376 (74476) ng·h/mL, respectively, for bedaquiline and 246 (103) ng/mL and 39540 (17220) ng·h/mL, respectively, for the M2 metabolite.

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 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. The plasma protein binding of its active metabolite, M2, in humans is at least 99.8%. In animals, bedaquiline and M2 are extensively distributed to most tissues, however, brain uptake is low.

Biotransformation

CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation and metabolism of 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 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 participants with moderate hepatic impairment (Child-Pugh B) demonstrated exposure to bedaquiline and M2 (AUC_{672h}) was 19% lower compared to healthy participants. 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
In paediatric patients aged 5 years to less than 18 years and weighing 15 kg to less than 30 kg, the average plasma exposure of bedaquiline (AUC_{168h}) at Week 24 is predicted to be 152 µg·h/mL (90% prediction interval: 54.3 to 313 µg·h/mL) when treated with the recommended weight-based dosing regimen. In paediatric patients weighing from 30 to 40 kg, the average plasma exposure of bedaquiline (AUC_{168h}) at Week 24 is predicted to be higher (average: 229 µg·h/mL; 90% prediction interval: 68.0 to 484 µg·h/mL) compared to adult patients. In paediatric patients aged 5 years to less than 18 years and weighing greater than 40 kg, the average plasma exposure of bedaquiline (AUC_{168h}) at Week 24 is predicted to be 165 µg·h/mL (90% prediction interval: 51.2 to 350 µg·h/mL) when treated with the recommended weight-based dosing regimen. The average plasma exposure of bedaquiline (AUC_{168h}) at Week 24 in adults was predicted to be 127 µg·h/mL (90% prediction interval: 39.7 to 249 µg·h/mL). The pharmacokinetics of SIRTURO in paediatric patients less than 5 years of age or weighing less than 15 kg have not been established.

Elderly patients
In a population pharmacokinetic analysis of tuberculosis 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.

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 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 tuberculosis patients treated with SIRTURO, no clinically relevant differences 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 patients with pulmonary 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 than 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 45 mg/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 mineralisation (partial recovery in males, and no recovery in females within 8 weeks after end of exposure). The NOAEL corresponds to a plasma AUC_{24h} of 13.1 and 35.6 µg·h/mL for bedaquiline (~0.7x clinical dose) and 10.5 and 16.3 µg·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

SIRTURO 20 mg tablet
Microcrystalline cellulose
Crospovidone
Silica, colloidal anhydrous
Hypromellose
Polysorbate 20
Sodium stearyl fumarate

SIRTURO 100 mg tablet
Lactose monohydrate
Maize starch
Hypromellose
Polysorbate 20
Microcrystalline cellulose
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

SIRTURO 20 mg tablets
3 years

SIRTURO 100 mg tablets
3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

SIRTURO 20 mg tablets
Store in the original container and keep the container tightly closed in order to protect from light and moisture. Do not remove desiccant.

SIRTURO 100 mg tablets
Store in the original container or package in order to protect from light.

6.5 Nature and contents of container

SIRTURO 20 mg tablets
White, opaque, high-density polyethylene (HDPE) bottle with child-resistant polypropylene (PP) closure with aluminium induction seal liner. Each bottle contains 60 tablets and silica gel desiccant.

SIRTURO 100 mg tablets
White HDPE bottle with child-resistant PP closure with aluminium induction seal liner containing 188 tablets.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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).

SIRTURO 20 mg tablet can also be administered through a feeding tube (8 French or greater) as follows:

- Disperse 5 tablets or less in 50 mL of non-carbonated water and mix well. Mixture should be white to almost white with visible particles expected.
- Administer through feeding tube immediately.
- Repeat with additional tablets until desired dose is reached.
- Rinse and flush with 25 mL of additional water to ensure no tablet residue is left in materials used for preparation or the feeding tube.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/901/001
EU/1/13/901/002
EU/1/13/901/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 March 2014
Date of latest renewal: 20 December 2022

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.