SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bedaquiline Tablets 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Bedaquiline fumarate equivalent to Bedaquiline..... 100 mg .

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL form

White to off white, round biconvex, uncoated tablets debossed with “J” & “47” on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

Bedaquiline is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adults and adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

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

Bedaquiline 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 Bedaquiline 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 Bedaquiline.

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

Posology

The recommended dosage of Bedaquiline is shown in the table below.

Table 1: Recommended dosage of Bedaquiline	
Population	**Dosing Recommendation**
Adults (18 years and older)	• 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).
Adolescents (12 years to less than 18 years of age and weighing at least 30 kg)	

Treatment duration

The total duration of treatment with Bedaquiline is 24 weeks. Data on longer treatment duration is very limited. In patients with extensive drug resistance, where Bedaquiline 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.

Missed doses

Patients should be advised to take Bedaquiline 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 Bedaquiline in elderly patients.

Hepatic impairment

No dose adjustment is necessary for Bedaquiline in patients with mild or moderate hepatic impairment. Bedaquiline should be used with caution in patients with moderate hepatic impairment. Bedaquiline 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, Bedaquiline should be used with caution.

Paediatric population

The safety and efficacy of Bedaquiline in children aged < 12 years or weighing less than 30 kg have not yet been established.

No data are available.

Bedaquiline may be included in the treatment regimen for adolescents greater than or equal to 12 years of age and weighing at least 30 kg with confirmed or with probable MDR-TB disease which is diagnosed based on clinical signs and symptoms of pulmonary MDR-TB, appropriate epidemiological context, and in line with international/local guidelines .

Method of administration

Bedaquiline should be taken orally with food, as administration with food increases oral bioavailability by about 2-fold. Bedaquiline tablets should be swallowed whole with water

4.3 Contraindications

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

4.4 Special warnings and precautions for use

There are no clinical data on the use of Bedaquiline 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 Bedaquiline 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

Bedaquiline was administered for 24 weeks in combination with a background regimen, more deaths occurred in the Bedaquiline treatment group than in the placebo group. The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with Bedaquiline treatment.

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.

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 . 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.

Bedaquiline 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

Bedaquiline 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 Bedaquiline with the background regimen. 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 Bedaquiline and/or any hepatotoxic background medicinal product should be discontinued.

Other hepatotoxic medicinal products and alcohol should be avoided while on Bedaquiline, 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. 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 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.

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. 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 adult patients not receiving antiretroviral (ARV) therapy. Those patients studied all had CD4+ cell counts greater than 250 x 10^6 cells/l.

Lactose intolerance and lactase deficiency

Bedaquiline 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 adult subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)]. Due to the possibility of a reduction of the therapeutic effect of bedaquiline due to a decrease in systemic exposure, co-administration of 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 adult 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.

Other antituberculosis medicinal products

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

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 in adults, 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 adult 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,Bedaquiline 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 in adults did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on co-administration of bedaquiline and antiretroviral agents in adult patients co-infected with human immunodeficiency virus and multi-drug resistant *Mycobacterium tuberculosis* are not available. 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 in adults, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual 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.

QT interval and concomitant clofazimine use

In an open label Phase IIb trial, mean increases in QTcF were larger in the 17 adult 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) .

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy:

There are limited data on the use of Bedaquiline in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

As a precautionary measure**,** avoid the use of Bedaquiline during pregnancy unless the benefit of therapy is considered to outweigh the risks.

Lactation:

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.

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 Bedaquiline therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

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

4.8 Undesirable effects

The most frequent ADRs (> 10.0% of patients) during treatment with bedaquiline in the controlled trials were nausea, arthralgia, headache, vomiting and dizziness.

Adverse drug reactions to bedaquiline. Adverse drug reactions are listed by system organ class (SOC) and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

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

Description of selected adverse reactions

Cardiovascular

Mean increases from baseline values in QTcF were observed from the first on-treatment assessment onwards. The largest mean increase from baseline values in QTcF during the 24

weeks of bedaquiline treatment was 15.7 ms (at week 18). After the end of bedaquiline treatment (i.e. after week 24), QTcF increases in the bedaquiline 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.

Patients with no treatment options received other QT-prolonging medicinal products used to treat tuberculosis, including clofazimine, concurrent use with bedaquiline resulted in additive

QT prolongation, proportional to the number of QT prolonging medicinal products in the treatment regimen.

Patients receiving bedaquiline 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

Increased transaminases:

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

Paediatric population

The safety assessment of bedaquiline is based on data from 15 adolescents greater than or equal to 14 years of age with confirmed or probable MDR-TB infection . Overall, there was no indication of any differences in the safety profile in these adolescents compared to that observed in the adult population.

4.9 Overdose

Cases of intentional or accidental acute overdose with bedaquiline were not reported during clinical trials.

There is no experience with the treatment of acute overdose with bedaquiline. 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.

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.

Commonly susceptible species

Mycobacterium tuberculosis

Inherently resistant organisms

Mycobacterium xenopi

Mycobacterium novocastrense

Mycobacterium shimoidei

Non-mycobacterial species

5.2 Pharmacokinetic properties

The pharmacokinetic properties of bedaquiline have been evaluated in adult healthy subjects and in multi-drug resistant tuberculosis-infected patients 14 years of age and older. 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

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.

Environmental Risk Assessment (ERA)

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate, Corn/Maize Starch, Hypromellose 2910, Polysorbate 20, Microcrystalline Cellulose, Croscarmellose Sodium, Colloidal Silicon Dioxide and Magnesium Stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life:

24 Months

6.4 Special precautions for storage :

Do not store above 30°C.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Container Pack : 188 Tablets

188 Tablets packed in round, white, HDPE container, 150cc HW, 38mm neck finish 38mm continuous thread closure with pulp and HS 123 white printed liner along with Absorbent cotton coil 12g/yard.

Blister pack:

6's Count

6 Tablets packed in Plain 25 µ Aluminum Foil/6-8 gsm HSL along with Cold Form foil (25 µ OPA/45 µ Alu /60 µ PVC) &pack such 12 blister in a carton along with pack insert.

10's Count

10 Tablets packed in Plain 25 µ Aluminum Foil/6-8 gsm HSL along with Cold Form foil (25 µ OPA/45 µ Alu /60 µ PVC) &pack such 10 blister in a carton along with pack insert.

28's Count
28 Tablets packed in Plain 25 µ Aluminum Foil/6-8 gsm HSL along with Cold Form foil (25 µ OPA/45 µ Alu /60 µ PVC) &pack such 7 blister in a carton along with pack insert.

6.6 Special precautions for disposal <and other handling>-

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/SUPPLIER>

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8. Market authorization number:

09452/09228/NMR/2021

9. DATE OF <Authorization> / <RENEWAL OF Authorization >

Feb 3, 2024

10. DATE OF REVISION OF THE TEXT

Reference list

https://www.medicines.org.uk/emc/product/3560/smpc/print
https://www.who.int/selection_medicines/committees/expert/20/applications/Bedaquiline_Janssen.pdf