Janssen Research & Development

Application for Inclusion of Bedaquiline 20 mg tablets on the WHO Model List of Essential Medicines (EML and EMLc)

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Prepared by: Janssen Research & Development, LLC
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Events
AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency Syndrome
AUC	Area under the (plasma concentration-time) curve
BR	Background Regimen
CI	Confidentiality Interval
DOT	Directly Observed Therapy
DR	Drug-Resistant
DS-TB	Drug Sensitive TB
DST	Drug Susceptibility Testing
EMA	European Medicines Agency
EML(c)	Essential Medicines List (children)
EU	European Union
FDA	Food and Drug Administration
GDF	Stop TB Global Drug Facility
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
IDA	International Dispensary Association
IQR	Interquartile Range
MDR-TB	Multidrug-resistant TB
M2	N-monodesmethyl metabolite
M.tuberculosis	*Mycobacterium tuberculosis*
NTP	National TB Program
PK	Pharmacokinetics
PP	Polypropylene
Pre-XDR-TB	Pre-extensively drug resistant TB
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RR-TB	Rifampicin-resistant TB
SAE	Serious Adverse Events
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SRA	Stringent Regulatory Authority
SRS	Strategic Rotating Stockpile
TB	Tuberculosis
US	United States
US PI	US Package Insert
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant TB

1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

Bedaquiline is a diarylquinoline and a novel anti-mycobacterial agent used as part of a combination therapy for the treatment of pulmonary tuberculosis (TB). Due to its novel mode of action, bedaquiline defines a new class of anti-TB compounds. In addition, the distinct target of bedaquiline minimizes the potential for cross-resistance with existing anti-TB drugs. The unique mechanism of action of bedaquiline involves a specific inhibition of mycobacterial adenosine 5' triphosphate synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*. The inhibition of adenosine 5' triphosphate synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.(1)

The WHO conducted a review of the available evidence on MDR-TB treatment in 2018 and, based on data emerging from the programmatic setting, issued a recommendation with a new hierarchy of medicines consisting of 3 groups. In the new recommendation, bedaquiline, the newer generation fluoroquinolones, and linezolid are included in the group A drugs to be prioritized for use in longer regimens for the treatment of MDR-TB and RR-TB in adults and children. (2) In addition, the WHO updated its guidelines on the use of short-course regimens in late 2019 to recommend a phasing out of injectable agents and replacing of the injectable component of the 9-12 month short-course regimen with bedaquiline. These recommendations are now reflected in the current WHO consolidated guidelines issued in 2020, and, as a result, bedaquiline is a key component of both short-course and longer treatment regimens for MDR-TB in adults and children.(3) Bedaquiline 100 mg tablets are included on the complementary list of Antituberculosis Medicines in the 21st WHO Model List of Essential Medicines as well as in the 7th WHO Model List of Essential medicines for children for use in the population 6 years and older (≥ 6 years).(4)

The spread of drug-resistant strains of *M. tuberculosis* is increasingly recognized as a major problem for children in countries with significant transmission of drug-resistant disease.(5)

In an analysis published in 2014, it was estimated that 31,948 (95% CI: 25,594 to 38,663) children developed MDR-TB globally in 2010. The estimated number [range] of incident MDR-TB cases in children was largest for the WHO Southeast Asia region (10,000 [4,993 to 15,568]) followed by the Western Pacific region (8,349 [5,639 to 11,610]), the European region (5,645 [4,206 to 7,463]), the African region (4,736 [2,829 to 6,848]), the Eastern Mediterranean region (2,417 [339 to 5,087]), and the Americas (606 [374 to 854]).(6)

The availability of the anti-MDR-TB drugs for children is therefore essential to successfully reduce the disease burden in children. The use of bedaquiline as part of a combination therapy to treat pulmonary MDR-TB avoids the use of injectable-containing regimens. Avoiding an injectable-containing regimen, which is associated with hearing loss (9), is particularly desirable in children, especially the very young, given the negative impact that hearing loss has on development.

Janssen addresses the unmet medical need in the paediatric MDR-TB treatment by the development of an age-appropriate and child friendly oral 20 mg tablet formulation offering

multiple options for administration. These 20 mg functionally scored tablets are dispersible in a small volume of water, which can then be mixed with beverage (e.g., water, milk products, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g., yogurt, apple sauce, mashed banana or porridge). They may also be crushed and mixed with food. In addition, dispersed tablets may be administered via a nasogastric tube. This 20 mg tablet can also be used by adults who have difficulty swallowing. The 20 mg tablet was evaluated in paediatric trial C211 in children ≥5 - <12 years of age and was shown to be generally well tolerated and had a safety profile that is comparable to the safety profile of bedaquiline per recommended dose in adults and adolescents who received the 100 mg tablet. In that same trial the 20 mg tablet was also shown to be palatable for children. The age appropriate 20 mg tablet is approved by US Food and Drug Administration (FDA) for the use in the population from 5 years and older and weighing at least 15 kg and is currently also under evaluation by the European Medicines Agency (EMA). The Applicant's global brand name of bedaquiline is SIRTURO®.

This application is to include bedaquiline 20 mg oral tablet on the complementary list of anti-MDR-TB drugs in the EML and EMLc and to extend the current age recommendation (children ≥ 6 years) to children ≥ 5 years old and weighing at least 15kg for the bedaquiline 100 mg oral tablet in the EMLc.

2. RELEVANT WHO TECHNICAL DEPARTMENT AND FOCAL POINT (IF APPLICABLE)

WHO Global TB department.

3. NAME OF ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION.

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4. INTERNATIONAL NONPROPRIETARY NAME (INN) AND ANATOMICAL THERAPEUTIC CHEMICAL (ATC) CODE OF THE MEDICINE

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

5. DOSE FORMS(S) AND STRENGTH(S) PROPOSED FOR INCLUSION, INCLUDING ADULT AND AGE-APPROPRIATE PAEDIATRIC DOSE FORMS/STRENGTHS (IF APPROPRIATE)

5.1. Product Information

Bedaquiline 20 mg tablets are supplied as uncoated white to almost white oblong functionally scored tablets with a score line on both sides, debossed with "2" and "0" on one side and plain on the other side.

Bedaquiline tablets are packaged in white high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closure with induction seal liner in the following configurations:

- 20 mg tablets – bottles of 60 tablets. Each bottle contains silica gel desiccant (NDC 59676702-60)

The bedaquiline 20 mg tablet is manufactured on behalf of Janssen Pharmaceutica NV by:

- Recipharm Pharmaservices Pvt Ltd., 34th KM, T-begur, Tumkur Road, Bangalore 562123, Bengaluru, Karnataka 562123, India. (Internationally)

6. WHETHER LISTING IS REQUESTED AS AN INDIVIDUAL MEDICINE OR AS REPRESENTATIVE OF A PHARMACOLOGICAL CLASS

Janssen requests inclusion of the bedaquiline 20 mg tablet on the EML and EMLc lists as an individual medicine, in addition to the 100 mg tablet formulation which is already on the EML and EMLc.

Bedaquiline is a diarylquinoline with in vitro activity against drug-sensitive TB (DS-TB), MDR-TB including pre-extensively drug resistant (pre-XDR-TB) and XDR-TB. Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. Pre-XDR TB is defined as in vitro resistance of the patient's isolate to: (1) isoniazid, (2) rifampin and (3) either a fluoroquinolone or at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin). XDR-TB is defined as in vitro resistance of the patient's isolate to: (1) isoniazid, (2) rifampin, (3) a fluoroquinolone and (4) at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).(41)

Due to its novel mode of action, bedaquiline defines a new class of anti-TB compounds; currently, no other drugs belonging to the same pharmacological class as bedaquiline are available.

This application is to include bedaquiline 20 mg oral tablet on the complementary list of anti-MDR-TB drugs in the EML and EMLc and to extend the current age recommendation (children ≥ 6 years) to children ≥ 5 years old and weighing at least 15kg for the bedaquiline 100 mg oral tablet in the EMLc.

7. TREATMENT DETAILS (REQUIREMENTS FOR DIAGNOSIS, TREATMENT AND MONITORING)

7.1. MDR-TB Treatment Options

In general, the development of therapeutic regimen recommendations for the treatment of MDR-TB in paediatrics is not standardized globally and national paediatric guidelines for MDR-TB are limited or non-existent in many countries with a high-burden of MDR-TB disease.(10) Treatment decisions are complex and selection of the regimen is typically individualized based on information from the source case, judicious use of second-line drugs taking into account expected or observed toxicities and observed drug susceptibility testing (DST) if available.(11) Therefore, the prescribing physician should refer to WHO (3) and/or national TB treatment guidelines, where available, for direction on selection and duration of the use of companion drugs in conjunction with bedaquiline.

The WHO conducted a review of the available evidence on MDR-TB treatment in 2018 and, based on data emerging from programmatic setting, issued a recommendation with a new hierarchy of medicines into 3 groups to guide the development of treatment regimens. In the new recommendation, bedaquiline, the newer generation fluoroquinolones, and linezolid are included in the group A drugs to be prioritized for use in longer regimens for the treatment of MDR-TB and RR-TB in adults and children. (2).

In addition, the WHO updated its guidelines on the use of short-course regimens in late 2019 to recommend a phasing out of injectable agents and replacing of the injectable component of the 9-12 month short-course regimen with bedaquiline.

These recommendations are now reflected in the current WHO consolidated guidelines issued in 2020, and, as a result, bedaquiline is a key component of both short-course and longer treatment regimens for MDR-TB in adults and children.(3)

The principles of MDR/XDR-TB treatment regimens in children are similar to those of adults and the same second-line drugs are generally used.

Children with culture-confirmed MDR-TB should be treated according to the DST result of their own isolate; while children with presumptive MDR-TB, based on contact with a known adult MDR-TB source case, should be treated according to the DST result of the source case's isolate. In children, as in adults, bedaquiline is to be used in combination with at least 3 drugs to which the subject's isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, treatment could be initiated with bedaquiline in combination with at least 4 other drugs to which the subject's isolate was likely to be susceptible. Upon completion of bedaquiline treatment, patients should continue to receive their background regimen (BR). It is recommended that bedaquiline is administered by directly observed therapy (DOT).

7.2. Recommended Dosage Regimen and Duration of Treatment

The recommended dosage of bedaquiline in adult patients and in children 5 years and older and weighing at least 15 kg is shown in the Table 1 and Table 2.

Table 1: Recommended Dosage of bedaquiline In Adult Patients[#]

Dosage Recommendation	
Weeks 1 and 2	**Weeks 3 to 24[a]**
400 mg (4 of the 100 mg tablets OR 20 of the 20 mg tablets) orally **once daily**	200 mg (2 of the 100 mg tablets OR 10 of the 20 mg tablets) orally **three times per week**
a = At least 48 hours between doses	
The total duration of treatment with bedaquiline in adults is 24 weeks. Bedaquiline tablets are administered with food.	

[#] US PI (40)

Table 2: Recommended Dosage of bedaquiline in Paediatric Patients (5 years and older and weighing at least 15 kg) [#]

Body Weight	Dosage Recommendation	
	Weeks 1 and 2	Weeks 3 to 24[a]
15 kg to less than 30 kg	200 mg (2 of the 100 mg tablets OR 10 of the 20 mg tablets) orally **once daily**	100 mg (1 of the 100 mg tablets OR 5 of the 20 mg oral tablets) orally **three times per week**
Greater than or equal to 30 kg	400 mg (4 of the 100 mg tablets OR 20 of the 20 mg tablets) orally **once daily**	200 mg (2 of the 100 mg tablets OR 10 of the 20 mg tablets) orally **three times per week**
a = At least 48 hours between doses.		
The total duration of treatment with bedaquiline in Paediatric patients is 24 weeks. Bedaquiline tablets are administered with food.		

[#] US PI (40)

7.3. Methods of Administration

The four different methods of administration of bedaquiline 20 mg tablet are outlined below. Each of the below administration method requires the tablets to be taken with food.

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

Administer bedaquiline 20 mg tablet whole or divided in half along the functional score line into two equal halves of 10 mg each. Administer bedaquiline 20 mg tablet with water.

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

For patients who have difficulty swallowing intact tablets, bedaquiline 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 products, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g., yogurt, apple sauce, mashed banana or porridge) as follows:

- Disperse tablets in water (maximum of 5 tablets in 5 mL of water) in a drinking cup.

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

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

Administration Through a Nasogastric Tube

Bedaquiline 20 mg tablet can be administered through a nasogastric 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 the nasogastric 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 nasogastric tube.

7.4. Use in Specific Populations

7.4.1. Paediatric Use

Bedaquiline, as part of combination therapy, is approved in the US for paediatric patients 5 years and older weighing at least 15 kg. The use in this paediatric population is supported by evidence from the study in adults together with additional pharmacokinetic and safety data from the single-arm, open-label, multi-cohort trial that enrolled 30 paediatric patients 5 years to less than 18 years of age with confirmed or probable MDR-TB infection who were to be treated for 24 weeks in combination with a background regimen.(43) The safety, effectiveness and dosage in paediatric patients less than 5 years of age and/or weighing less than 15 kg have not been established.

7.4.2. Geriatric Use

Because of limited data, differences in outcomes or specific risks cannot be ruled out for patients 65 years of age and older.

7.4.3. Hepatic Impairment

The pharmacokinetics of bedaquiline were assessed after single-dose administration to adult patients with moderate hepatic impairment (Child-Pugh B). Based on these results, no dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic impairment. bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients only when the benefits outweigh the risks. Clinical monitoring for bedaquiline-related adverse reactions is recommended monthly while on treatment, and as needed.

7.4.4. Renal Impairment

Bedaquiline has mainly been studied in adult patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial (less than or equal to 0.001%). No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis, bedaquiline should be used with caution. Monitor adult and paediatric patients for adverse reactions of bedaquiline when administered to patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis.

8. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

8.1. Epidemiological Information on Disease Burden

8.1.1. Tuberculosis in General

Tuberculosis is a transmissible disease caused by M. tuberculosis that commonly affects the lungs but can also spread to other organs.(13) In 2017, there were an estimated 10.0 million prevalent TB cases (range: 9.0-11.1 million) and approximately 1.6 million people (range: 1.5-1.7 million) died from this curable disease in 2017.(14)

8.1.2. Multi-Drug Resistant Tuberculosis

Incidence and Prevalence

Multidrug-resistant tuberculosis (MDR-TB) has been reported in all regions of the world. The true burden of the disease is likely to be underestimated due to limitations of survey data. The prevalence of drug-resistant TB is usually presented as the proportion of TB cases exhibiting resistance to anti-TB drugs rifampicin and isoniazid.

The MDR-TB burden largely falls on three countries (India, China and the Russian Federation) which together account for nearly half of the global cases. (2) According to the WHO annual report on Global Tuberculosis Control, there were an estimated 484,000 (range 417,000 to 556,000) new cases of MDR-TB/rifampicin-resistant (RR)-TB globally in 2018, with cases of MDR-TB accounting for 78% of the total.(2)

MDR-TB has been reported in all regions of the world. The prevalence of drug-resistant (DR)-TB is usually presented as the proportion of TB cases exhibiting resistance to anti-TB drugs rifampicin and isoniazid.

Globally, an estimated 3.4% (95% confidence interval [CI]: 2.5% to 4.4%) of new TB cases and 18% (95% CI: 7.6% to 31%) of re-treatment TB cases have MDR/RR-TB. Among the 30 high MDR-TB burden countries, the proportion of MDR/RR-TB cases among new cases and previously treated cases of TB reported ranged from 1.3% (Kenya) to 37% (Belarus) and from 4.4% (Kenya) to 71% (Russian Federation), respectively. The highest proportions of MDR-TB are found in countries in Eastern Europe and Central Asia. An increasing number of TB cases that are resistant to isoniazid and rifampicin plus a fluoroquinolone and at least one injectable second-line drug, known as extensively drug-resistant (XDR)-TB, have been reported. XDR-TB has been documented in 131 countries globally. Surveillance data from 128 countries and five territories revealed the average proportion of MDR-TB cases with XDR-TB was 6.2% (95% CI: 4.4% to 8.2%).(2)

Routine surveillance data on MDR-TB among children are not available globally. Confirmation of TB in children is difficult because bacteriologic confirmation is often not achieved, especially in younger children. Case detection in young children is poor due to the paucibacillary nature of the disease in children (less than 10% of pulmonary TB in young children is AFB smear-positive), and because they cannot expectorate sputum on demand.(20, 21) As a result, a high proportion of child TB cases are diagnosed on the basis of clinical criteria without microbiological confirmation. This absence of microbiological confirmation restricts both the ability to directly measure the incidence of TB in children and to routinely assess the risk of MDR-TB among these cases.(22) This absence of microbiological confirmation restricts both the ability to directly measure the incidence of TB in children (20) and to routinely assess the risk of MDR-TB among these cases.(23)

Based on several mathematical models, approximately 3% of children with TB are estimated to have MDR-TB.(20, 24) Global estimates of the burden of MDR-TB in children range from 25,000 to 32,000 incident cases annually.(6, 25)

In an analysis published in 2014, it was estimated that 31,948 (95% CI: 25,594 to 38,663) children developed MDR-TB globally in 2010.(6) The estimated number [range] of incident MDR-TB cases in children was largest for the WHO Southeast Asia region (10,000[4,993 to 15,568]) followed by the Western Pacific region (8,349 [5,639 to 11,610]), the European region (5,645 [4,206 to 7,463]), the African region (4,736 [2,829 to 6,848]), the Eastern Mediterranean region (2,417 [339 to 5,087]), and the Americas (606 [374 to 854]).(6)

A more recent analysis estimated that 58,000 children developed isoniazid-mono resistant TB, 7,600 RR-TB, 25,000 MDR-TB, and 1,200 XDR-TB in 2014 (Dodd 2016). Incidences varied substantially between regions. Globally, it was estimated that a median 6.9% (interquartile range [IQR] 6.6 to 7.1) of incident TB disease in children was isoniazid-mono resistant, 0.9% (IQR 0.8

to 1.0) was RR-TB, and 2.9% (IQR 2.7 to 3.1) was MDR-TB. Of the children with MDR-TB, a median 4.7% (IQR4.3to 5.1) was estimated to be XDR-TB.(25)

The estimates of incident TB in children in 2014, by drug-resistance type and WHO region are presented in Table 3.

Table 3: Estimates of Incident TB in Children in 2014, by Drug-resistance Type and WHO Region

	Isoniazid-monoresistant	Rifampicin-monoresistant	Multidrug-resistant	Extensively drug-resistant
WHO region				
African	16,800 (10,800-25,700)	2,890 (1,860-4,460)	8,230 (5,190-12,800)	245 (151-396)
Americas	1,170 (743-1,810)	113 (69-191)	525 (330-816)	51 (31-86)
Eastern Mediterranean	6,640 (4,280-10,100)	1,290 (811-2,040)	3,340 (2,120-5,160)	185 (110-311)
European	1,610 (1,030-2,510)	179 (113-280)	2,120 (1,320-3,310)	168 (105-265)
Southeast Asia	21,200 (13,700-33,000)	1,820 (1,180-2,840)	6,370 (4,100-9,910)	199 (134-322)
Western Pacific	9,760 (6,320-14,700)	1,080 (705-1,690)	3,540 (2,320-5,400)	244 (159-376)
Global	**58,300 (38,300-87,800)**	**7,630 (5,010-11,500)**	**24,800 (16,100-37,400)**	**1,160 (757-1,770)**

Adapted from Dodd 2016

Furthermore, in the aforementioned analysis by Dodd et al, it was estimated that of the 67 million children infected with TB globally, nearly 5 million had isoniazid-monoresistant infections, 600,000 had RR-TB, 2 million had MDR-TB, and 100,000 had XDR-TB.(25)

The estimates of the numbers of children infected with TB in 2014, by drug-resistance type and WHO region are presented in Table 4.

Table 4: Estimates of the Numbers of Children Infected with TB in 2014, by Drug-resistance Type and WHO Region

	Isoniazid-monoresistant	Rifampicin-monoresistant	Multidrug-resistant	Extensively drug-resistant
WHO region				
African	1,040,000 (707,000-1,360,000)	180,000 (137,000-233,000)	489,000 (373,000-640,000)	15,800 (11,200-22,100)
Americas	97,600 (73,300-130,000)	9,560 (6,760-14,200)	44,500 (33,000-60,900)	4,480 (3,030-6,720)
Eastern Mediterranean	583,000 (437,000-775,000)	106,000 (75,330-152,000)	288,000 (212,000-390,000)	15,400 (10,500-22,800)
European	166,000 (123,000-227,000)	17,800 (13,200-24,200)	219,000 (160,000-304,000)	17,300 (12,500-24,100)
Southeast Asia	1,950,000 (1,470,000-2,570,000)	162,000 (122,000-215,000)	586,000 (442,000-769,000)	18,300 (12,900-26,100)
Western Pacific	901,000 (696,000-1,170,000)	103,000 (79,100-135,000)	344,000 (264,000-445,000)	24,700 (18,600-32,300)
Global	**4,810,000 (3,750,000-6,160,000)**	**594,000 (463,000-763,000)**	**2,000,000 (1,560,000-2,580,000)**	**101,000 (78,100-131,000)**

Adapted from Dodd 2016

In terms of demographic analysis in children, in an analysis of WHO surveillance data, it was found that MDR-TB prevalence in children is similar to those of adults in many countries. In addition, the risk of MDR-TB infection is similar between children younger than 5 years of age and children 5 to 14 years of age. (26)

Globally in 2018, there were an estimated 581,000 and 538,000 incident cases of TB in males and females, respectively, under 15 years of age. The male-to-female ratio for children was close to one in all WHO regions. (2)

MDR-TB in children, especially in those less than 5 years of age, is an infectious disease usually transmitted through household contacts with MDR-TB infection. Older children and adolescents may develop cavitary, adult-type TB, which is associated with higher bacillary loads and therefore more natural DR mutations. Mismanagement of TB treatment in these children may lead to the development of drug-resistance.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The emergence of drug-resistance in TB is a major concern. The global distribution of MDR-TB is particularly heterogeneous. *M.tuberculosis* develops drug-resistance through genetic mutations which are then amplified by selective pressures due to misuse of anti-TB drugs.(15) When the prevalence of DR-TB is high enough, direct transmission of DR strains can then become the predominant mechanism of propagating MDR-TB in any given area.(16)

Until early 2016, MDR-TB patients required a treatment duration of 2 years on average with the substantially more toxic and less potent second-line anti-TB drugs. Cure rates were lower and mortality higher than for DS-TB, particularly if patients are coinfected with HIV. According to the latest WHO data, 56% of MDR/RR-TB patients and 39% of XDR-TB patients were successfully treated, reflecting high mortality rates and loss to follow-up. (2)

Mortality and case-fatality estimates are uncertain partly due to incomplete coverage of global drug-resistance surveillance and the lack of direct measurements of MDR-TB deaths. An estimated 214,000 (range 133,000 to 295,000) deaths caused by MDR/RR-TB occurred in 2018, including those with HIV infection.(2) According to treatment outcomes reported by the WHO for the 2015 cohort, 15% of MDR/RR-TB patients and 26% of XDR-TB patients died. The high overall mortality reflects poor diagnostic and treatment capacity for MDR-TB globally. Even for patients that make it into good treatment programs, overall mortality still exceeds 10%, with a range of 8% to 21%.(17) Two independently conducted meta-analyses from 2009, each including approximately 30 studies in MDR-TB, found death as a reported outcome in 11% of treated patients.(18, 19) Another meta-analysis reflecting data from 9,153 individual patients reported a mortality rate of 15.2% (95% CI: 14.5% to 16.0%).(39) Patients who died were significantly older, more likely to be HIV-coinfected, with more extensive disease, and/or had prior therapy.

Children usually have transmitted resistance, as the disease is normally paucibacillary, making acquired resistance less likely.(27) The diagnosis and the choice of the appropriate treatment of MDR-TB in children is challenging as it can be difficult to bacteriologically confirm the diagnosis because of difficulties in collecting respiratory samples in younger children and in children who frequently have paucibacillary disease. Few children globally are diagnosed and appropriately treated for MDR-TB. Only approximately 1,000 children have been reported to receive MDR-TB treatment at any time in the past.(8) As minimal literature is available on mortality for children with MDR-TB, a recent literature review of mortality in children with TB estimated that 22% (95% CI: 18% to 26%) of children with TB died in the pretreatment era.(28) Given the high number of children with MDR-TB who are untreated, mortality is likely to be significant. Based on limited data on treatment outcomes in children, it appears that those who are identified, diagnosed, and treated with appropriate therapy have good outcomes. In a systematic review of 8 studies reporting the treatment of MDR-TB in children (n=315), the pooled estimate for treatment success was 82%.

Across all studies, 5.9% died, and 6.2% were lost to follow-up. The most common drug-related adverse events (AEs) were nausea and vomiting. Other serious AEs (SAEs) were hearing loss, psychiatric effects, and hypothyroidism.(22) Another meta-analysis of data from 975 children from 18 countries reported 78% of patients treated for MDR-TB had treatment success, 9% died, 2% failed treatment, and 11% were lost to follow-up.(8) A study in South Africa examining predictors of childhood MDR-TB treatment outcomes identified associations between death and malnutrition, extrapulmonary TB, and HIV.(27) Another study in Peru reported that children faced significantly higher risk of death or treatment failure if they had severe disease or were underweight.(29) These findings are consistent with the Harausz et al. meta-analysis where

investigators also found that malnutrition and not being treated for HIV during TB treatment significantly increased the risk of poor outcomes.(8)

Important Comorbidities

Important comorbidities in patients with MDR-TB include HIV/Acquired Immunodeficiency Syndrome (AIDS), diabetes mellitus, and depression. Important comorbidities in paediatric patients with MDR-TB infection include HIV/AIDS and malnutrition.

8.2. Assessment of Current Use

Based on the total distribution of 4,787,177 grams of finished product distributed from launch to 31 August 2020, the estimated cumulative post-marketing exposure to bedaquiline is 254,637 completed treatment courses with the 100 mg tablet.

As the 20 mg tablet has only been available since the USA FDA approval on 27 May 2020, the total distribution of this formulation is limited so far.

8.3. Likely Impact of Treatment on the Disease

There is a growing number of children worldwide accessing anti-tuberculosis drugs for MDR-TB; however, there are very few child-friendly formulations. For paediatric use, dispersible tablets offer distinct advantages over liquid formulations and other approaches. This is particularly relevant for TB, where stability, long shelf-life and reduced manufacturing, transport and storage costs are all critical to ensuring that drugs are accessible and affordable.(34)

Since May 2020, bedaquiline is approved in the United States of America for the use in children 5 years and older and weighing above 15 kg. The available bedaquiline 20 mg tablet in conjunction with the WHO classification of bedaquiline as a priority drug for adults and children for the treatment of MDR-TB, is expected to play a crucial role in the treatment of MDR-TB in the younger children.

The age appropriate dispersible and palatable 20 mg tablet makes an important contribution to the treatment of MDR-TB children (for which not many age appropriate formulations are available) and hence to the reduction of the disease burden in paediatrics.

The bedaquiline 20 mg dispersible formulation allows flexibility in terms of administration methods as described in the Section 7.2. In both adults and children, the ability to administer bedaquiline dispersible tablets via a nasogastric tube provides additional flexibility for dosing in patients who are not able to swallow in general.

In addition, the bioavailability of the 100-mg tablet was not altered when crushing and re-suspension prior to intake, supporting also pediatric administration.(44)

9. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

9.1. Identification of Clinical Evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Clinical evidence is based on the clinical studies conducted by the Applicant, which is also reflected in the US PI (US package insert) and EU SmPC (EU Summary of Product Characteristics).

The literature search has been conducted taking in the account the clinical trials with bedaquiline since 2012. The relevant publications on the available clinical evidence are listed below.

Achar, J., Hewison, C., Cavalheiro, A.P., Skrahina A., Cajazeiro J., Nargiza, P., at all. **"Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis"** *Emerg Infect Dis. 2017 Oct; 23(10): 1711–1713*

Moodliar R., Aksenova V., Frias M. V. G., Van De Logt J., Rossenu S., Birmingham E., et al. "**Bedaquiline for multi drug-resistant, including extensively or pre-extensively drug-resistant, pulmonary mycobacterium tuberculosis in children**." *American Journal of Respiratory and Critical Care Medicine (2020)* **201**(1), Abstract.

9.2. Summary of Available Data (appraisal of quality, outcome measures, summary of results)

The clinical development of bedaquiline started in 2005 and includes an extensive program of Phase 1 studies that provided a description of the pharmacokinetic (PK) characteristics of bedaquiline and its drug-drug interaction potential, its short-term safety and tolerability profile, as well as recommendations for the administration and dosing regimen.

Bedaquiline has been shown to be effective in the patient populations with MDR-TB enrolled in Phase 2b clinical trials TMC207-C208, TMC207-C209.

The paediatric data are generated in the TMC207-C211 (NCT02354014), which is an ongoing, open-label, Phase 2 trial designed to evaluate the PK, safety, tolerability, and antimycobacterial activity of bedaquiline in combination with a BR of MDR-TB medications in children and adolescents 0 months to <18years of age who have confirmed or probable pulmonary MDR-TB. The data presented in this application are from the Week 24 primary analyses of Cohort 1 (≥12 to <18 years, using bedaquiline 100 mg tablets and Cohort 2 (≥5 to <12 years, using bedaquiline 20 mg tablets).

The totality of the data from bedaquiline clinical development supports the use of bedaquiline as part of combination therapy for the treatment of MDR-TB in adults and paediatric patients 5 years and above and weighing at least 15 kg:

- can reduce the time to sputum culture conversion and improve the proportion of subjects with culture conversion at endpoint

- has a safety profile that was characterized across the spectrum of subjects with pulmonary MDR-TB
- has ADRs that can be managed,
- provides a valuable addition to address an urgent unmet medical need.

9.3. Summary of Available Estimates of Comparative Effectiveness

9.3.1. Clinical Pharmacology

9.3.1.1. Pharmacodynamics

Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (4-fold to 6-fold lower) compared to the parent compound. However, M2 plasma concentrations appeared to correlate with QT prolongation.

9.3.1.2. Pharmacokinetics

The pharmacokinetic parameters of bedaquiline in adult MDR-TB patients at the recommended dosing regimen of bedaquiline (400 mg for 2 weeks followed by 200 mg three times per week for 22 weeks*) in combination with a BR at week 8 have been evaluated in the Stage 1 of clinical trial C208 and are provided in Table 5.

Table 5: Pharmacokinetic Parameters of Bedaquiline Following Repeat Dose Administration of Bedaquiline at the Recommended Dosing Regimen to Adult MDR-TB

Pharmacokinetic Parameter	Bedaquiline Mean (SD)
AUC24h (ng*h/mL)	25,863 (13,259)
Cmax (ng/mL)	1,659 (722)
Tmax (h)*	5 (3-8)
Cmin (ng/mL)	654 (498)
SD=Standard deviation *Median (range)	

*dosing in adults used bedaquiline 100 mg tablets

9.3.1.3. Absorption

After single oral dose administration of bedaquiline, maximum plasma concentrations (C_{max}) are typically achieved at approximately 5 hours post-dose. C_{max} and the area under the plasma concentration-time curve (AUC) increased proportionally up 700 mg (1.75 times the 400 mg loading dose). Administration of bedaquiline with a standard meal containing approximately 22 grams of fat (558 total Kcal) increased the relative bioavailability by approximately 2-fold compared to administration under fasted conditions. bedaquiline should be taken with food to enhance its oral bioavailability. Distribution The plasma protein binding of bedaquiline is greater

than 99.9%. The volume of distribution in the central compartment is estimated to be approximately 164 Liters.

9.3.1.4. Elimination

After reaching C_{max}, bedaquiline concentrations decline tri-exponentially. The mean terminal elimination half-life of bedaquiline and the N-monodesmethyl metabolite (M2) is approximately 5.5 months. This long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues. Metabolism CYP3A4 was the major CYP isoenzyme involved in the in vitro metabolism of bedaquiline and the formation of the N-monodesmethyl metabolite (M2).

9.3.1.5. Excretion

Based on preclinical studies, bedaquiline is mainly excreted in feces. The urinary excretion of unchanged bedaquiline was less than or equal to 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant.

9.3.1.6. Hepatic Impairment

After single-dose administration of 400 mg bedaquiline to 8 adult patients with moderate hepatic impairment (Child-Pugh B), mean exposure to bedaquiline and M2 (AUC_{672h}) was approximately 20% lower compared to healthy subjects. Bedaquiline has not been studied in patients with severe hepatic impairment.

9.3.1.7. Renal Impairment

Bedaquiline has mainly been studied in adult patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial (less than or equal to 0.001%). In a population pharmacokinetic analysis of MDR-TB adult patients treated with bedaquiline 200 mg three times per week, creatinine clearance was not found to influence the pharmacokinetic parameters of bedaquiline. It is therefore not expected that mild or moderate renal impairment will have a clinically relevant effect on the exposure to bedaquiline. However, in patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis bedaquiline concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As bedaquiline is highly bound to plasma proteins, it is unlikely that it will be significantly removed from plasma by hemodialysis or peritoneal dialysis.

9.3.1.8. Sex

In a population pharmacokinetic analysis of MDR-TB adult patients treated with bedaquiline no clinically relevant difference in exposure between men and women were observed.

9.3.1.9. Race/Ethnicity

In a population pharmacokinetic analysis of MDR-TB adult patients treated with bedaquiline, systemic exposure (AUC) to bedaquiline was found to be 34% lower in Black patients than in patients from other race categories. This lower exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed

in clinical trials of MDR-TB. Furthermore, response rates were comparable in patients of different race categories that completed 24 weeks of bedaquiline treatment.

9.3.1.10. HIV Co-infection

There are limited data on the use of bedaquiline in HIV coinfected patients in clinical trials of MDR-TB. Furthermore, response rates were comparable in patients of different race categories that completed 24 weeks of bedaquiline treatment. HIV Co-infection: There are limited data on the use of bedaquiline in HIV coinfected patients.

9.3.1.11. Geriatric Population

There are limited data on the use of bedaquiline in tuberculosis patients 65 years of age and older. In a population pharmacokinetic analysis of MDR-TB adult patients treated with bedaquiline, age was not found to influence the pharmacokinetics of bedaquiline.

9.3.1.12. Paediatric Population

Paediatric Patients 12 Years to Less Than 18 Years of Age With MDR-TB

The pharmacokinetic parameters of bedaquiline in 15 paediatric patients (body weight at baseline: 38 to 75 kg) using the bedaquiline 100 mg tablets formulation who received the same adult dosage regimen of bedaquiline (400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks) in combination with a BR were comparable to those in adults. There was no impact of body weight on bedaquiline pharmacokinetics in this cohort.

Paediatric Patients 5 Years to Less Than 12 Years of Age With MDR-TB

Fifteen MDR-TB paediatric patients (body weight at baseline: 14 to 36 kg) received bedaquiline (200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks) using the bedaquiline 20 mg tablet formulation in combination with a BR. Of these 15 paediatric patients, complete pharmacokinetic data were obtained for 10 patients at the aforementioned dosage regimen of bedaquiline. In 9 of these 10 paediatric patients who weighed at least 15 kg at baseline, the mean bedaquiline Cmax and AUC24h were similar to that of adult MDR-TB patients receiving the recommended adult dosage regimen.

See Table 6 for a summary of the pharmacokinetic parameters in paediatric patients 5 years to less than 18 years of age.

Table 6: Pharmacokinetic Parameters of Bedaquiline Following Repeat Dose Administration of Bedaquiline to Paediatric MDR-TB Patients 5 to less than 18 years of age at Week 12 Administered with Food (N=25)

Pharmacokinetic Parameter	Bedaquiline Mean (SD)	
	14 years to less than 18 years (N=15)	5 years to less than 12 years (N=10)
AUC_{24h} (ng•h/mL)	26,300 (10,300)	32,200 (16,300)
C_{max} (ng/mL)	1,800 (736)	2,430 (1,670)
T_{max} (h)*	4 (2-8)	4 (2-8)
C_{min} (ng/mL)	544 (263)	461 (173)

SD=Standard Deviation
* Median (range)

9.3.2. Clinical Effectiveness

9.3.2.1. Adult Patients

The clinical development of bedaquiline started in 2005 and includes an extensive program of Phase1 studies that provided a description of the pharmacokinetic (PK) characteristics of bedaquiline and its drug-drug interaction potential, its short-term safety and tolerability profile, as well as recommendations for the administration and dosing regimen.

The pediatric clinical development program consists of the development of an appropriate formulation for younger children who may not be able to swallow tablets and the Phase 2 pediatric Study TMC207-C211 in children and adolescents 0 months to <18 years of age with confirmed or probable pulmonary MDR-TB, in agreement with the EU Paediatric Investigation Plan (PIP). While adolescents (≥12 to <18 years of age) in Study TMC207-C211 were dosed with the adult tablet and dose regimen, an age-appropriate formulation was developed. The 20-mg scored (TMC207; Bedaquiline) (C211 W24-C2) tablet (G008) has been evaluated in Study TMC207-C211 from Cohort 2 onwards (children <12 years of age).

Since the exposures of bedaquiline and M2 have been shown to be similar in adults and children with comparable safety profiles (based on AEs, laboratory abnormalities and other safety assessments) and the expected management of MDR-TB is similar between children and adults, the benefits on TB treatment outcome of bedaquiline in pediatric subjects aged ≥5 to <12 years with confirmed or probable MDR-TB infection can be extrapolated from the adult data.

A short-term Phase 2a Proof-of-Principle Trial TMC207-C202 (C202), was conducted to provide clinical confirmation in subjects with DS-TB of the in vitro findings of antibacterial activity of bedaquiline. This trial is not included in the all clinical trials population in this application due to differences in trial design (active-controlled) and population (subjects with DS-TB) compared with the 2 Phase 2b trials TMC207-C208 (C208) and TMC207-C209 (C209). The conditional marketing authorization of bedaquiline 100-mg tablets, granted on 05 March 2014 in the EU and

the accelerated approval registration in the US are based on the data from the 2 completed Phase 2b trials in adult subjects (C208 and C209) with the recommended dose and tablet formulation.

Trial C208 was a randomized, double-blind, placebo-controlled, Phase 2b trial designed to evaluate the antibacterial activity, safety, and tolerability of bedaquiline in subjects with newly diagnosed sputum smear-positive pulmonary infection with MDR-TB. Subjects randomized to the active treatment arm received bedaquiline 400 mg once daily for 2 weeks, followed by 200 mg 3 times a week for 6 weeks (Stage 1) or 22 weeks (Stage 2) in combination with a standard 5-drug, second-line anti-TB regimen.

In the former study (Stage 1), patients were randomized to either bedaquiline and other drugs used to treat MDR-TB (bedaquiline treatment group) (n=23) or placebo and other drugs used to treat MDR-TB (placebo treatment group) (n=24). Twenty-one patients randomized to the bedaquiline treatment group and 23 patients randomized to the placebo treatment group had confirmed MDR-TB based on patients' baseline *M. tuberculosis* isolate obtained prior to randomization. The bedaquiline treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 8. At Weeks 8 and 24, the differences in culture conversion proportions were 38.9% (95% CI: [12.3%, 63.1%] and p-value: 0.004), 15.7% (95% CI: [-11.9%, 41.9%] and p-value: 0.32), respectively.

In the latter study (Stage 2), 79 patients were randomized to the bedaquiline arm and 81 to the placebo arm. A final evaluation was conducted at Week 120. Sixty-seven patients randomized to bedaquiline and 66 patients randomized to placebo had confirmed MDR-TB, based on susceptibility tests (taken prior to randomization) or medical history if no susceptibility results were available, and were included in the efficacy analyses. Demographics were as follows: 63% of the study population was male, with a median age of 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%.

Time to sputum culture conversion was defined as the interval in days between the first dose of study drug and the date of the first of two consecutive negative sputum cultures collected at least 25 days apart during treatment. In the Stage 2 part of the trial, the bedaquiline treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 24. Median time to culture conversion was 83 days for the bedaquiline treatment group compared to 125 days for the placebo treatment group. Table 7 shows the proportion of patients with sputum culture conversion at Week 24 and Week 120.

Table 7: Culture Conversion Status in Patients with MDR-TB at Week 24 and Week 120 in TMC207-C208 Stage 2 Study

Microbiologic Status	SIRTURO (24 weeks) + combination of other antimycobacterial drugs N=67	Placebo (24 weeks) + combination of other antimycobacterial drugs N=66	Difference [95% CI] p-value
Week 24			
Sputum Culture Conversion	78%	58%	20.0% [4.5%, 35.6%] 0.014
Treatment failure*	22%	42%	
Died	1%	0%	
Lack of conversion	21%	35%	
Discontinuation	0%	8%	
Week 120**			
Sputum Culture Conversion	61%	44%	17.3% [0.5%, 34.0%] 0.046
Treatment failure*	39%	56%	
Died	12%	3%	
Lack of conversion/relapse	16%	35%	
Discontinuation	10%	18%	

* A patient's reason for treatment failure was counted only in the first row for which a patient qualifies.
** Patients received 24 weeks of SIRTURO or placebo for the first 24 weeks and received a combination of other antimycobacterial drugs for up to 96 weeks.

TMC207-C209 (NCT00910871) was an open-label, Phase 2b, uncontrolled study to evaluate the safety, tolerability, and efficacy of bedaquiline as part of an individualized MDR-TB treatment regimen in 233 patients with sputum smear-positive (within 6 months prior to screening) pulmonary MDR-TB. Both newly diagnosed and treatment-experienced subjects were allowed to enroll. Subjects received bedaquiline 400mg once daily for 2 weeks, followed by 200 mg 3 times a week for 22 weeks. Upon completion of the 24-week treatment with bedaquiline, all patients continued to receive their BR in accordance with national TB program treatment guidelines. A final evaluation was conducted at Week 120. Treatment responses to bedaquiline at week 120 were generally consistent with those from TMC207-C208.

Janssen's current clinical development program for bedaquiline includes an ongoing Phase 3 trial (the STREAM Stage 2 Trial [TBC3007], sponsored by Vital Strategies, the North American affiliate of International Union Against Tuberculosis and Lung Disease [The Union] and conducted under an agreement with Janssen), and the abovementioned ongoing Phase 2 trial in children and adolescents aged 0 months to <18 years with confirmed or probable MDR-TB (C211).

9.3.2.2. Paediatric Patients

TMC207-C211 (NCT02354014) is an ongoing, open-label, Phase 2 trial designed to evaluate the PK, safety, tolerability, and antimycobacterial activity of bedaquiline in combination with a BR of MDR-TB medications in children and adolescents 0 months to <18years of age who have

confirmed or probable pulmonary MDR-TB. The data presented in this application are from the Week 24 primary analyses of Cohort 1 (≥12 to <18 years) and Cohort 2 (≥5 to <12 years).

Paediatric Patients (12 Years to Less Than 18 Years of Age)

Fifteen patients ages 14 years to less than 18 years of age were enrolled in the first cohort. The median age was 16 years, 80% were female, 53% were Black, 33% were White and 13% were Asian. Bedaquiline was administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks using the 100 mg tablet in combination with an individualized MDR-TB treatment option. In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 75.0% (6/8 patients) at Week 24.

Paediatric Patients (5 Years to Less Than 12 Years of Age)

Fifteen patients ages 5 years to 10 years of age were enrolled in the second cohort. The median age was 7 years, 60% were female, 60% were Black, 33% were White and 7% were Asian. The body weight ranged from 14 kg to 36 kg; only one patient weighing 14 kg was enrolled. Bedaquiline was administered as 200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks using the 20 mg tablet in combination with an individualized MDR-TB treatment option. In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 100% (3/3 patients) at Week 24.

Population PK Analysis of Bedaquiline Dosage

A model-based analysis of bedaquiline was performed on data from the 15 adolescents (Cohort 1) and 15 children (5 to <12 years, Cohort 2) enrolled in Study TMC207-C211. A nonlinear mixed-effect model was used for model-based predictions of individual bedaquiline PK parameters, which were derived using all available concentration data, and for each subject a maximum a posteriori estimate of individual AUC_{168h} was derived at Weeks 12 and 24. The exposure metrics obtained were compared with the simulated AUC_{168h} obtained in adults from previous studies at Weeks 12 and 24 for a maintenance dosage of 200 mg 3 times per week. The model-based analyses used a previously developed population PK model developed across 9 adult clinical studies in both healthy subjects and subjects with MDR-TB. To account for age-related changes in adolescents and children (5 to <12 years), allometric scaling of clearance and volume parameters based on total body weight was included.

Goodness-of-fit plots suggested that the performance of the model was acceptable and could describe the data with no bias and with good precision. The mean AUC_{168h} values at Week 12 and Week 24 were compared with the protocol-defined 60% to 140% range for the adult geometric mean AUC_{168h} (86,200 to 201,000 ng.h/mL) at steady state for a bedaquiline dosage of 200 mg 3 times per week.

To investigate the appropriateness of the bedaquiline dosages used in adolescents (Cohort 1) and children (5 to <12 years, Cohort 2), AUC_{168h} was determined after administration of the loading and maintenance doses in Study TMC207-C211. A total of 1,000 subjects in each cohort were sampled from the virtual paediatric subject database. AUC_{168h} values at Weeks 12 and 24 were computed from the simulation of 168 timepoints using a linear-trapezoidal method. The 95% range of AUC_{168h} from the simulations was determined across total body weights and overlaid with the model-derived AUC_{168h} values and the 95% range of adult AUC_{168h} values at Weeks 12 and 24, respectively. Additionally, AUC24h values at Weeks 2 and 12 were computed from the simulations and graphically compared with the observed AUC24h values.

- **Determination of Exposure Metrics and Model Parameters**

The geometric mean AUC_{168h} values for bedaquiline in adolescents and children (5 to <12 years) at Week 12 (127,000 and 126,000 ng.h/mL, respectively) and Week 24 (146,000 and 133,000 ng.h/mL, respectively) were contained within 60% to 140% of the adult AUC_{168h} geometric mean at steady state (86,200 to 201,000 ng.h/mL). The increase in exposure observed in adolescents between Weeks 12 and 24 indicates that bedaquiline had not reached steady state at Week 12. A model-based analysis determined an average ratio of AUC_{168h} at Week 24: AUC_{168h} at steady state of approximately 0.85. The majority of model-predicted AUC_{168h} values at Weeks 12 and 24 were within the 95% range of the adult simulations for the same week, confirming the choice of the dosage within both cohorts (ie, 400 mg/day as a loading dose and 200 mg 3 times per week as a maintenance dose for adolescents, and 200 mg/day as a loading dose and 100 mg 3 times per week as a maintenance dose for children from 5 to <12 years).

- **Recommended Dose Regimens for Adolescents and Children (5 to <12 Years)**

When simulating the AUC_{168h} of bedaquiline at Weeks 12 and 24 for adolescents in Study TMC207-C211 (Cohort 1) using the approved adult dosage (ie, 400 mg/day as a loading dose and 200 mg 3 times per week as a maintenance dose), the mean values obtained for the weight bands of 30 to 40 kg, 40 to 50 kg, and 50 to 60 kg fell within 60% to 140% of the geometric mean AUC_{168h} in adults at steady state that was used as the target exposure in Study TMC207-C211When simulating the AUC_{168h} of bedaquiline at Weeks 12 and 24 for children (5 to <12 years) in Study TMC207-C211 (Cohort 2) using half the approved adult dosage (ie, 200 mg/day for the first 2 weeks followed by 100 mg 3 times per week, as tested in study TMC207-C211), the mean values obtained for the weight bands of 15 to 20 kg and 20 to 30 kg fell within 60% to 140% of the geometric mean AUC_{168h} in adults at steady state that was used as the target exposure in Study TMC207-C211. Therefore, for children (5 to <12 years), half the adult dose (as tested in Cohort 2 of Study TMC207-C211), either as the 20-mg or 100-mg tablet, delivers similar bedaquiline exposure for the weight range of 15 to 30 kg to that achieved in adults.

The integrated PK model does not contain age as a covariate for the age range tested to date (including adults and all subjects recruited in Study TMC207-C211 from 5 to <18 years). Simulations for Cohorts 1 and 2 in this study were largely driven by body weight and age did not impact the outcome of these simulations. Therefore, the results for Cohorts 1 and 2 were combined.

The fact that age itself does not impact bedaquiline exposure (other than indirectly through the correlation with body weight, which is a significant parameter in the PK model) is in line with expectations because maturation of cytochrome P450 3A4, the main metabolizing enzyme for bedaquiline, is generally complete in this age range. Cytochrome P450 3A4/5 activity is low at birth and reaches adult values in the first years of life, so no further maturation would be expected in the age range of 5 to 18 years.

When simulating bedaquiline exposures across age groups (expressed as AUC_{168h}) at Weeks 12 and 24, the following dose regimens were tested: the approved adult dose (as tested in Cohort 1 of Study TMC207-C211) in adolescents and also in children (5 to <12 years) with a body weight of at least 30 kg, and half the approved adult dose (as tested in Cohort 2 of Study TMC207-C211) in children (5 to <12 years) and also in adolescents with a body weight of 15 to 30 kg. The results show that for all weight bands with the doses proposed for adolescents and children (5 to <12 years), the mean bedaquiline exposure is within 60% to 140% of the adult geometric mean exposure at steady state, which is the prespecified target exposure in Study TMC207-C211.

Based on the above considerations, the following recommended dose regimens for bedaquiline in the treatment of MDR-TB in adolescents and children (ie, paediatric patients from 5 to less than 18 years) are:

- 400 mg once daily during the first 2 weeks, followed by 200 mg 3 times per week for 22 weeks, in paediatric patients from 5 to less than 18 years weighing at least 30 kg.
- 200 mg once daily during the first 2 weeks, followed by 100 mg 3 times per week for 22 weeks, in paediatric patients from 5 to less than 18 years weighing 15 to less than 30 kg.

10. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF SAFETY

10.1. Estimate of Total Patient Exposure to Date

Based on the total distribution of 4,787,177 grams of finished product distributed from launch to 31 August 2020, the estimated cumulative post-marketing exposure to bedaquiline is 254,637 completed treatment courses with the 100 mg tablet. As the 20 mg tablet has only been available since the US approval on 27 May 2020, the total distribution of this formulation is limited so far.

The all clinical trials adult population includes two trials: the Phase 2b randomized, blinded trial previously described (Trial C208 [Stage 1 and 2]), and the Phase 2b, open-label trial (Trial C209). Together, the all clinical trials adult population comprises 335 subjects, including 102 bedaquiline-treated subjects from Trial C208 plus 233 bedaquiline-treated subjects from Trial C209.

The all clinical trials paediatric population includes Cohort 1 (≥12 to <18 years) and Cohort 2 (≥5 to <12 years) of Trial C211. Exposure to bedaquiline in the all clinical trials paediatric population Cohort 1 and Cohort 2 is fifteen subjects for each of these two cohorts.

10.2. Description of the Adverse Effects/Reactions and Estimates of their Frequency

Adverse reactions for bedaquiline were identified from the pooled safety data from 335 bedaquiline exposed patients who received 8 weeks (C208 Stage 1) and 24 weeks (C208 Stage 2 and C209) at the proposed dose. The basis of assessment of causality between the adverse drug reactions and bedaquiline was not restricted to these trials, but also on review of the pooled Phase 1 and Phase 2a safety data in adults. The most frequent adverse drug reactions (> 10.0% of patients) during treatment with bedaquiline in the controlled trials were nausea (35.3% in the bedaquiline 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%).

Adverse drug reactions to bedaquiline reported from controlled trials in 102 adult patients treated with bedaquiline are presented in the Table 8 .

Table 8 [#]: Tabulated List of Adverse Reactions

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).		
**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).		

[#] EU SmPC (41)

The sponsor performs safety signal detection activities related to bedaquiline use on an ongoing basis. This includes review of pediatric cases received from all sources, including clinical studies and spontaneously reported cases. No new safety signal related to use in pediatric patients has been identified. Additionally, the sponsor has reviewed events reported to FAERS in patients aged 0-17. The most frequently reported events (preferred terms) in the FAERS database are “off label use,” and “medication error,” which likely reflect use in an unapproved population. “Electrocardiogram QT prolonged” and “cough” were the most common adverse events reported, each in 6 patients. All other adverse events were reported five or fewer times.

10.3. Summary of Available Data (Appraisal of Quality, Summary of Results)

The general safety profile is described in section of 10.2 and below the events of special interest are described.

10.3.1. Cardiac Electrophysiology

Bedaquiline prolongs the QTc interval. In a placebo-controlled, double-blind, randomized trial (TMC201-C208), in adults, the mean increases in QTcF, corrected using the Fridericia method, were greater in the bedaquiline treatment group compared to the placebo treatment group from the first week of treatment (9.9 ms at Week 1 for bedaquiline and 3.5 ms for placebo). The largest mean increase in QTcF during the 24 weeks of bedaquiline treatment was 15.7 ms compared to 6.2 ms with placebo treatment (at Week 18). After bedaquiline treatment ended, the QTcF gradually decreased, and the mean value was similar to that in the placebo group by study week 60.

In the Phase 2b, open-label study (C209), where adult patients with no treatment options received other QT-prolonging drugs used to treat tuberculosis, including clofazimine, concurrent use with bedaquiline resulted in additive QTcF prolongation, proportional to the number of QT-prolonging drugs in the treatment regimen. Patients taking bedaquiline with no other QT-prolonging drug developed a mean QTcF increase over baseline of 23.7 ms with no QTcF segment duration in excess of 480 ms, whereas patients taking at least two other QT-prolonging drugs developed a mean QTcF prolongation of 30.7 ms over baseline, and resulted in QTcF segment duration in excess of 500 ms in one patient.

10.3.2. Mortality

In the randomized Phase IIb study (C208, Stage 2), a higher rate of deaths was seen in the bedaquiline treatment group (12.7%; 10/79 patients) compared to the placebo treatment group (3.7%; 3/81 patients). One death in the bedaquiline group and one death in the placebo group were reported after the week 120 window. In the bedaquiline 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 bedaquiline patients were alcohol poisoning, hepatitis/hepatic cirrhosis, septic shock/peritonitis, cerebrovascular accident and motor vehicle accident. One of the ten deaths in the bedaquiline group (due to alcohol poisoning) occurred during the 24-week treatment period. The other nine deaths among those treated with bedaquiline occurred after completion of treatment with this agent (range 86-911 days post bedaquiline; median 344 days). The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with bedaquiline treatment. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other medicinal products used to treat tuberculosis, HIV 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 2b, 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 patient who died

of tuberculosis had not converted or had relapsed. The causes of death in the remaining patients varied.

Additional information on treatment outcomes including mortality for bedaquiline containing regimens have been reported recently from different programmatic settings.

An analysis of mortality from the South African TB program was completed by the WHO as part of a systematic review on the available evidence on the use of bedaquiline and indicated a 50-60% reduction in mortality in subjects treated with a regimen including bedaquiline compared to those treated with a non- bedaquiline containing regimen. It includes data from 1,596 subjects treated with bedaquiline as part of the regimen, and 23,539 treated during same period in the program, but not receiving bedaquiline. Human immunodeficiency virus co-infection rates were high in the entire cohort (67.9% of subjects overall). It is noteworthy that the bedaquiline containing group reflected primarily subjects with higher degrees of resistance and limited treatment options, ie, pre-XDR and XDR-TB. The mortality rate in the bedaquiline group was 7.6%, compared to 18.2% mortality in the non- bedaquiline cohort. This difference was statistically significant. Additional analyses including a Cox regression with propensity score adjustment yielded similar results, all consistent with a beneficial effect.(30)

A further retrospective analysis of the data in the South African MDR-TB program including 19,617 patients, of which 1,016 received bedaquiline, showed that bedaquiline treatment was associated with a reduction in the risk of all-cause mortality for patients with MDR- or RR-TB (hazard ratio 0.35, 95% CI: 0.28–0.46) and XDR-TB (0.26, 0.18-0.38) compared with standard regimens.(31)

A recent individual patient data meta-analysis investigated outcomes of treatment success and death with the use of individual drugs in over 12,000 MDR-TB patients from 50 studies in 25 countries. The analysis showed both a significant association between reduced mortality and use of bedaquiline (adjusted risk difference [-0.14, 95% CI: -0.19 to -0.10]), as well as a positive association between treatment success and use of bedaquiline (adjusted risk difference [0.10, 95% CI: 0.05 to 0.14]).(32)

10.3.3. Safety Profile in Paediatric Population

The safety assessment of bedaquiline is based on the Week 24 analysis from 30 paediatric patients in an ongoing, single-arm, open-label, multi-cohort trial, C211.

10.3.3.1. Paediatric Patients (12 Years to Less Than 18 Years of Age)

The first cohort was designed to enroll patients 12 years to less than 18 years of age (fifteen patients 14 years to less than 18 years of age were enrolled) with confirmed or probable pulmonary MDR-TB infection who received bedaquiline (400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks) in combination with a BR. Overall, safety was generally consistent with observations from previous clinical studies with bedaquiline in adults. The most common adverse reactions were arthralgia in 6/15 (40%) patients, nausea in 2/15 (13%) patients,

and abdominal pain in 2/15 (13%) patients. Among the 15 patients, no deaths occurred during treatment with bedaquiline. Observed laboratory abnormalities were comparable to those in adults.

10.3.3.2. Paediatric Patients (5 Years to Less Than 12 Years of Age)

The second cohort was designed to enroll patients 5 years to less than 12 years of age (fifteen patients aged 5 years to less than 11 years of age were enrolled) with confirmed or probable pulmonary MDR-TB infection who received bedaquiline (200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks) in combination with a BR. The most common adverse reactions were related to increased transaminases including AEs of hepatoxocity (3/15, 33%), that led to discontinuation of bedaquiline in three patients. Elevations in liver enzymes were reversible upon discontinuation of bedaquiline and some of the BR drugs. Among these 15 paediatric patients, no deaths occurred. The selected bedaquiline dosing regimen for 24 weeks as part of MDR-TB therapy was generally safe and anticipated toxicities, were manageable with careful monitoring and modifications of the TB treatment regimen.

11. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS OF THE MEDICINE

In general, the addition of bedaquiline to the standard of care for treatment of MDR-TB in adults was shown as a cost-effective option in the projected benefits observed in trial to real-world practices. Multiple studies done in different programmatic settings demonstrated the economic value of bedaquiline in improving cost per routine outcomes including disability-adjusted life-years (DALYs), quality-adjusted life-years (QALYs), DALY averted as well as potential cost-saving (34-38). Currently available evidence evaluating economic value of bedaquiline are limited to be studied in adults, not yet in paediatrics.

A tiered pricing strategy for sustainable and affordable access to bedaquiline is being implemented globally. This comprehensive Access & Affordability approach is in view of the unique public health considerations of MDR-TB. It is Janssen's policy to communicate prices after regulatory approval and discussions with local health authorities.

Bedaquiline 20 mg is accessible through GDF for 25,53 USD for a bottle of 60 tablets. This amounts to a price of 200 USD for a full treatment cycle (470 tablets/24 weeks) in children weighing 15 kg to less than 30 kg administering half the adult dose. Bedaquiline, 20 mg tablet is also indicated for adults and/or adolescents who have trouble swallowing, for which a complete treatment cycle would require 940 tablets (33).

Janssen Pharmaceutica, N.V. has a long-term agreement with the International Dispensary Association (IDA) for the supply of bedaquiline by order and account of the Stop TB Global Drug Facility (GDF), which is an initiative that provides a unique package of services, including technical assistance in TB drug management and monitoring of TB drug use to patients in need in over 135 countries. To improve lead time for deliveries to countries GDF has setup a Strategic Rotating Stockpile (SRS), with unassigned stock always available at IDA.

12. SUMMARY OF REGULATORY STATUS AND MARKET AVAILABILITY OF THE MEDICINE

The bedaquiline 20 mg tablet is approved by the US FDA as part of combination therapy of pulmonary TB due to MDR-TB in children 5 to less than 18 years of age, weighing at least 15 kg, and is currently under the review by EMA. Additional registrations are planned to be initiated worldwide prioritized for high burden countries.

Ministries of health, through their national TB programs, of nearly 140 countries, can procure bedaquiline through the Stop TB Partnership's GDF, a Geneva-based centralized mechanism for sourcing TB medicines that sits within the United Nations Operations infrastructure. Janssen Pharmaceutica N.V. has established a long-term agreement with the IDA, a procurement agent for the GDF, for the supply of bedaquiline. GDF provides a unique complement of services, including market shaping of an otherwise fragile market, technical assistance in TB drug management and monitoring of TB drug use, as well as procurement of only stringent regulatory authority approved and/or WHO prequalified drugs. GDF has processes in place to ensure that countries with patients in need and where bedaquiline is not registered are able to waive registration as a precondition to import.

13. AVAILABILITY OF PHARMACOPOEIAL STANDARDS (BRITISH PHARMACOPOEIA, INTERNATIONAL PHARMACOPOEIA, UNITED STATES PHARMACOPOEIA, EUROPEAN PHARMACOPOEIA)

There are no compendial monographs established for bedaquiline at this time.

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