



U.S. FDA Approves New Pediatric Formulation of SIRTURO® (bedaquiline) as Part of Combination Therapy to Treat Children with Pulmonary Multidrug-Resistant Tuberculosis

May 27, 2020

NEW BRUNSWICK, NJ, May 27, 2020 — The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the U.S. Food and Drug Administration (FDA) has granted approval for a new pediatric formulation of SIRTURO® (bedaquiline). SIRTURO® is now indicated for use as part of combination therapy in the treatment of adult and pediatric patients (5 years and older and weighing at least 15 kg) with pulmonary multidrug-resistant tuberculosis (MDR-TB). In the U.S., the medicine should be reserved for use when an effective treatment regimen cannot otherwise be provided.

This indication received accelerated approval based on time to sputum culture conversion. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. SIRTURO® should not be used for the treatment of latent TB infection, extra-pulmonary or drug-sensitive TB, or for the treatment of infections caused by non-tuberculous mycobacteria. The safety and efficacy of SIRTURO® in the treatment of HIV-infected patients with MDR-TB have not been established, as clinical data are limited.

Today's decision marks the first regulatory approval for the pediatric formulation of SIRTURO® and is a key component of Johnson & Johnson's global pediatric research and development (R&D) program for the medicine. The new 20 mg tablet can be administered with water for patients who are able to swallow the intact tablet and taken with food. For patients who have difficulty swallowing intact tablets, the tablet can be dispersed in water and administered. To aid with administration, the dispersed mixture in water can be further mixed with a beverage or soft food. Alternatively, the tablet can be crushed and mixed with soft food immediately prior to use and administered.

"The first-ever approval of a pediatric formulation of bedaquiline is a significant advancement for children with multidrug-resistant tuberculosis," said **Martin Fitchet, M.D., Global Head, Global Public Health, Johnson & Johnson**. "TB is already an often-overlooked area in global health, and children with the disease are especially vulnerable. Modernizing pediatric treatment is a critical step toward reducing the suffering of these young patients and ending TB once and for all."

When SIRTURO® first received accelerated approval from the U.S. FDA for use in eligible adult patients in 2012, it was the first novel TB medicine in more than 40 years. In 2019, the FDA granted approval for SIRTURO® 100 mg tablets as part of combination therapy in adolescent patients (12 to less than 18 years of age and weighing at least 30 kilograms (66 pounds)) with pulmonary MDR-TB, when an effective treatment regimen cannot otherwise be provided. Further research is ongoing in children aged two to four, and in infants younger than two years old.

TB is the world's deadliest infectious disease, claiming approximately 1.5 million lives in 2018 alone – more than HIV and malaria combined. [\[i\]](#) While TB most often affects adults in their most productive years, in 2018, an estimated 1.1 million children became ill with TB worldwide and more than 200,000 died. According to the World Health Organization, however, these are likely underestimates of the true burden of the disease in children. [\[ii\]](#) These grim statistics underscore the urgent need for effective pediatric TB treatments.

"In the last 10 years, we have seen great advances in innovation for tuberculosis, especially for the hardest to treat forms," said **Ruxandra Draghia-Akli, M.D., Ph.D., Global Head, Global Public Health R&D, Janssen Research & Development, LLC**. "Johnson & Johnson is proud to be driving this research and development for patients of all ages. This latest accomplishment for our bedaquiline pediatric program will provide a new tool to address MDR-TB in vulnerable populations."

Today's FDA approval is supported by evidence from a single-arm, open-label, Phase 2 study that enrolled pediatric patients aged 5 to less than 12 years of age with confirmed or probable pulmonary MDR-TB infection who were treated at half the adult dose with the SIRTURO® 20mg tablet for 24 weeks in combination with a background regimen for the treatment of MDR-TB. The application for the pediatric formulation obtained priority review from the FDA.

INDICATIONS AND USAGE

SIRTURO® (bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adult and pediatric patients (5 years and older and weighing at least 15 kg) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO® for use when an effective treatment regimen cannot otherwise be provided.

This indication is approved under accelerated approval based on time to sputum culture conversion. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitations of Use

Do not use SIRTURO® for the treatment of:

- Latent infection due to *Mycobacterium tuberculosis*
- Drug-sensitive tuberculosis
- Extra-pulmonary tuberculosis
- Infections caused by non-tuberculous mycobacteria

The safety and efficacy of SIRTURO[®] in the treatment of HIV-infected patients with MDR-TB have not been established as clinical data are limited.

IMPORTANT SAFETY INFORMATION

WARNINGS: INCREASED MORTALITY AND QT PROLONGATION

INCREASED MORTALITY

- An increased risk of death was seen in the SIRTURO[®] treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial in adults. Only use SIRTURO[®] in patients 5 years of age and older when an effective treatment regimen cannot otherwise be provided.

QT PROLONGATION

- QT prolongation can occur with SIRTURO[®]. Use with drugs that prolong the QT interval may cause additive QT prolongation. Monitor ECGs. Discontinue SIRTURO[®] if significant ventricular arrhythmia or if QTcF interval prolongation of greater than 500 ms develops.

Warnings and Precautions

Increased Mortality: An increased risk of death was seen in the SIRTURO[®] treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial in adults (based on the 120 week visit window). One death occurred during the 24 weeks of administration of SIRTURO[®]. The imbalance in deaths is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat tuberculosis, HIV status, or severity of disease could be observed. Only use SIRTURO[®] in patients 5 years of age and older when an effective treatment regimen cannot otherwise be provided.

QT Prolongation: SIRTURO[®] prolongs the QT interval. Obtain an ECG before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with SIRTURO[®]. Obtain serum potassium, calcium, and magnesium at baseline and correct if abnormal. Monitor electrolytes if QT prolongation is detected. SIRTURO[®] has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

The following may increase the risk for QT prolongation when patients are receiving SIRTURO[®]: use with other QT prolonging drugs including fluoroquinolones and macrolide antibacterial drugs and the antimycobacterial drug, clofazimine; a history of Torsade de Pointes; a history of congenital long QT syndrome; a history of or ongoing hypothyroidism; a history of or ongoing bradyarrhythmias; a history of uncompensated heart failure; serum calcium, magnesium, or potassium levels below the lower limits of normal.

If necessary, bedaquiline treatment initiation could be considered in these patients after a favorable benefit risk assessment and with frequent ECG monitoring.

Discontinue SIRTURO[®] and all other QT prolonging drugs if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of greater than 500 ms (confirmed by repeat ECG).

If syncope occurs, obtain an ECG to detect QT prolongation.

Risk of Development of Resistance to Bedaquiline: A potential for development of resistance to bedaquiline in *Mycobacterium tuberculosis* exists. Bedaquiline must only be used in an appropriate combination regimen for the treatment of pulmonary MDR-TB to reduce the risk of development of resistance to bedaquiline.

Hepatotoxicity: In clinical trials, more hepatic-related adverse reactions were reported in adults with the use of SIRTURO[®] plus other drugs to treat tuberculosis compared to other drugs used to treat tuberculosis without the addition of SIRTURO[®]. Alcohol and other hepatotoxic drugs should be avoided while on SIRTURO[®], especially in patients with impaired hepatic function. Hepatic-related adverse reactions have also been reported in pediatric patients 5 years of age and older.

Monitor symptoms (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline, monthly while on treatment, and as needed. Test for viral hepatitis and discontinue other hepatotoxic medications if evidence of new or worsening liver dysfunction occurs. Discontinue SIRTURO[®] if:

- aminotransferase elevations are accompanied by total bilirubin elevation greater than two times the upper limit of normal
- aminotransferase elevations are greater than eight times the upper limit of normal
- aminotransferase elevations are greater than five times the upper limit of normal and persist beyond two weeks

Drug Interactions

CYP3A4 Inducers/Inhibitors: Bedaquiline is metabolized by CYP3A4 and its systemic exposure and therapeutic effect may therefore be reduced during co-administration with inducers of CYP3A4. Avoid co-administration of strong CYP3A4 inducers such as rifamycins (ie, rifampin, rifapentine, and rifabutin) or moderate CYP3A4 inducers such as efavirenz, during treatment with SIRTURO[®]. Co-administration of SIRTURO[®] with strong

CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions. Therefore, avoid the use of strong CYP3A4 inhibitors used for more than 14 consecutive days while on SIRTURO[®], unless the benefit of treatment with the drug combination outweighs the risk. Appropriate clinical monitoring for SIRTURO[®]-related adverse reactions is recommended.

Use in Specific Populations

Pregnancy

Risk Summary: Available data from published literature of SIRTURO[®] use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks associated with active tuberculosis during pregnancy. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to oral administration of bedaquiline to pregnant rats and rabbits during organogenesis at exposures up to 6 times the clinical dose based on AUC comparisons.

Clinical Considerations: *Disease-associated Maternal and/or Embryo/Fetal Risk* Active tuberculosis in pregnancy is associated with adverse maternal and neonatal outcomes including maternal anemia, caesarean delivery, preterm birth, low birth weight, birth asphyxia, and perinatal infant death.

Lactation

Risk Summary: There is no information regarding the presence of bedaquiline in human milk. Minimal data are available on the effects of the drug on the breastfed infant. No data are available on the effects of the drug on milk production. Bedaquiline is concentrated in the milk of rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SIRTURO[®] and any potential adverse effects on the breastfed infant from SIRTURO[®] or from the underlying maternal condition.

Pediatric Use: The safety, effectiveness and dosage of SIRTURO[®] in pediatric patients less than 5 years of age and/or weighing less than 15 kg have not been established.

Renal Impairment: SIRTURO[®] 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, SIRTURO[®] should be used with caution. Monitor adult and pediatric patients for adverse reactions of SIRTURO[®] when administered to patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis.

Adverse Reactions

Adult: Adverse reactions that occurred more frequently than placebo during treatment with SIRTURO[®] included: nausea (38% vs 32%), arthralgia (33% vs 22%), headache (28% vs 12%), hemoptysis (18% vs 11%), chest pain (11% vs 7%), anorexia (9% vs 4%), transaminases increased (9% vs 1%), rash (8% vs 4%), and blood amylase increased (3% vs 1%).

Pediatric:

The safety assessment of bedaquiline is based on the Week 24 analysis from 30 pediatric patients in an ongoing, single-arm, open-label, multi-cohort trial, (Study 4).

Pediatric 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 SIRTURO[®] (400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 22 weeks) in combination with a background regimen.

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 SIRTURO[®]. Observed laboratory abnormalities were comparable to those in adults.

Pediatric 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 SIRTURO[®] (200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks) in combination with a background regimen.

The most common adverse reactions were related to elevations in liver enzymes (5/15, 33%), and led to discontinuation of SIRTURO[®] in three patients. Elevations in liver enzymes were reversible upon discontinuation of SIRTURO[®] and some of the background regimen drugs. Among these 15 pediatric patients, no deaths occurred during treatment with SIRTURO[®].

Please read [full Prescribing Information](#), including [Boxed Warnings](#) and [Medication Guide](#) for more details.

About the Bedaquiline Global Pediatric Development Program

As part of the company's commitment to the continued clinical development of bedaquiline, Janssen is conducting a Phase 2 pediatric pharmacokinetic and safety study, C211, with four cohorts of patients in different age groups.

The FDA approval of the use of 100mg tablets of bedaquiline in adolescents (≥12 to <18 years and weighing at least 30 kg (66lb)) was supported by the results from Cohort 1 of the study. The FDA approval of the use of the 20mg pediatric formulation of bedaquiline in children (≥5 to <12 years and weighing at least 15 kg (33lb)) was supported by the results from Cohort 2 of the study. Enrollment of Cohort 3 (≥2 to <5 years old) is underway, and Cohort 4 (<2 years) will begin enrolling once key data from Cohort 3 of the study becomes available to select the appropriate dose for Cohort 4.

Janssen has also filed the application of the pediatric formulation and the data in children (≥5 to <12 years and weighing at least 15 kg) to the European Medicines Agency (EMA), with a European Commission decision anticipated by early 2021. Pediatric regulatory filings for bedaquiline are ongoing or planned in other countries as well, including high-burden countries.

Learn more about TMC207-C211 at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02354014) (identifier: [NCT02354014](https://clinicaltrials.gov/ct2/show/study/NCT02354014)).

About TB & MDR-TB

Tuberculosis (TB) is the world's deadliest infectious disease. Nearly one-quarter of the world's population — 1.7 billion people — are infected with *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. In most of them, the infection is in a latent state. But in 2018, 10 million people developed active tuberculosis and approximately 1.5 million people died of the disease.^[i]

Multidrug-resistant TB (MDR-TB) is a particularly complicated form of the bacterial infection and is characterized by resistance to at least two of the most powerful drugs in the first-line treatment regimen (isoniazid and rifampicin). Globally, MDR-TB is a growing threat. In 2018, there were nearly 400,000 new cases of MDR-TB, and drug-resistant TB now accounts for approximately one-third of all deaths from antimicrobial resistance (AMR).^[ii]

About Johnson & Johnson's Global Commitment to TB

Johnson & Johnson has been a committed partner in the fight against TB for more than two decades. When bedaquiline received its initial accelerated approval by the FDA in 2012 to treat MDR-TB in adults, as part of combination therapy, it was the first targeted medicine with a novel mechanism of action against TB in more than 40 years. Today, it is approved for use in 64 countries, with access pathways identified for all United Nations (UN) Member States. In total, more than 210,000 courses of bedaquiline have been delivered to 141 countries, including the 30 countries with the highest burdens of MDR-TB.

In September 2018, Johnson & Johnson [announced a comprehensive 10-year initiative](#) in support of the United Nations Sustainable Development Goal target of ending the TB pandemic by 2030. With the goal of saving an estimated 1.8 million lives and preventing 12 million new TB infections in the next decade, Johnson & Johnson is working with partners to improve detection of undiagnosed TB cases, broaden access to bedaquiline for MDR-TB, and accelerate R&D to discover next-generation TB treatments. Further, in October 2019, J&J announced a [\\$500 million, four-year investment](#) to support the discovery, development and delivery of new medicines and vaccines to combat TB and HIV.

Johnson & Johnson will be undertaking a series of collaborations with multilaterals and non-governmental organizations focused on improving case finding and diagnosis of pediatric patients in several high-burden countries, once COVID-19 circumstances allow.

Learn more about our work on TB at www.jnj.com/TB.

About Johnson & Johnson

At Johnson & Johnson, we believe good health is the foundation of vibrant lives, thriving communities and forward progress. That's why for more than 130 years, we have aimed to keep people well at every age and every stage of life. Today, as the world's largest and most broadly-based healthcare company, we are committed to using our reach and size for good. We strive to improve access and affordability, create healthier communities, and put a healthy mind, body and environment within reach of everyone, everywhere. We are blending our heart, science and ingenuity to profoundly change the trajectory of health for humanity. Learn more at www.jnj.com. Follow us at [@jniglobalhealth](https://twitter.com/jniglobalhealth).

[i] Interagency Coordination Group on Antimicrobial Resistance. *No Time to Wait: Securing the Future From Drug-Resistant Infections Report to the Secretary-General of the United Nations*. Last accessed July 2019. Available at: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1

About the Janssen Pharmaceutical Companies

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal.

++

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding SIRTURO[®] (bedaquiline). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of the Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining

regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2019, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

[1] World Health Organization. Global Tuberculosis Report 2019. Last accessed April 2020. Available at: https://www.who.int/tb/publications/global_report/en/

[1] World Health Organization. Child and Adolescent TB. Last accessed April 2020. Available at: <https://www.who.int/tb/areas-of-work/children/en/>

[1] Interagency Coordination Group on Antimicrobial Resistance. *No Time to Wait: Securing the Future From Drug-Resistant Infections Report to the Secretary-General of the United Nations*. Last accessed July 2019. Available at: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1

Media Contacts:

Jessica Freifeld
jfreifel@its.jnj.com
+1 917-520-1198

Ronan Collins
rcollin5@its.jnj.com
+47 488 425 00

Investor Contacts:

Chris DeOrefice
+1 732-524-2955

Jennifer McIntyre
+1 732-524-3922