

## World Health Organization Issues Interim Guidance on Bedaquiline

<p>Press Release</p>

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RARITAN, N.J., June 17, 2013 /PRNewswire/ -- Janssen Research & Development, LLC (Janssen) today welcomes the World Health Organization (WHO) interim policy guidance on the use of bedaquiline (trade name SIRTUO(TM) in the U.S.) in the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) as part of combination therapy in adults. The guidance culminates a rigorous review process by internal and external TB experts convened by the WHO and drew upon available Phase 2 safety and efficacy data, a cost-effectiveness assessment and independent analysis to review the six-month surrogate endpoint.

"Janssen welcomes the WHO's unprecedented rapid review of bedaquiline on the basis of Phase 2b trial data. We are working with a number of regulatory agencies to bring bedaquiline to patients who need it most," said Paul Stoffels, M.D., Chief Scientific Officer and Worldwide Chairman, Pharmaceuticals, Johnson & Johnson.

Bedaquiline is indicated as part of combination therapy in adults ( $\geq 18$  years) with pulmonary MDR-TB. Reserve bedaquiline for use when an effective treatment regimen cannot otherwise be provided. Bedaquiline should be administered by directly observed therapy (DOT). This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB. The safety and efficacy of bedaquiline for the treatment of drug-sensitive TB and latent infection due to *Mycobacterium tuberculosis* has not been established. In addition, there are no data on the treatment with bedaquiline of extrapulmonary TB (e.g., central nervous system). Therefore, use of bedaquiline in these settings is not recommended.

The prescribing information for bedaquiline includes Boxed Warnings regarding increased risk of death and occurrence of QT prolongation. The Warnings and Precautions section provides additional information regarding these risks and includes risk of hepatic-related adverse drug reactions, drug interactions, use in HIV-TB co-infected patients and treatment failure. The most common adverse drug reactions were nausea, arthralgia and headache. Additional adverse events were hemoptysis and chest pain. Please see Important Safety Information below for more details.

The WHO interim policy guidance is based on 24-week data from the Phase 2 clinical development program of Study 1 and Study 2 (TMC207-C209 and TMC207-C208), which includes an open-label study and a controlled, randomized trial that evaluated the safety and efficacy of bedaquiline versus

placebo in the treatment of adult patients with pulmonary MDR-TB in combination with a background regimen. Study 2 was a smaller placebo controlled study designed similarly to Study 1 except that bedaquiline or placebo was given for only 8 weeks instead of 24 weeks. Additionally the WHO requested an independent analysis to further review the six-month surrogate endpoint.

"We need a dedicated, cross-sector collaboration to fully address this public health challenge," said Adrian Thomas, Vice President, Global Market Access & Commercial Strategy Operations. "Janssen is continuing discussions with a range of organizations dedicated to advancing public health on how to best facilitate access to bedaquiline in low- and middle- income countries."

The U.S. FDA granted accelerated approval to bedaquiline in December 2012 based on the surrogate endpoint of time to sputum culture conversion. Janssen has filed regulatory submissions with the European Medicines Agency, and health authorities in several countries, including South Africa, China, Thailand and India. In addition, Janssen's commercial partner for Russia and CIS countries, JSC Pharmstandard, has filed a regulatory submission in Russia.

With a novel mechanism of action, bedaquiline inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.

## INDICATION

SIRTURO(TM) (bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults ( $\geq 18$  years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO(TM) for use when an effective treatment regimen cannot otherwise be provided. SIRTURO(TM) should be administered by directly observed therapy (DOT). This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB.

### Limitations of Use:

The safety and efficacy of SIRTURO(TM) for the treatment of latent infection due to *Mycobacterium tuberculosis* has not been established. The safety and efficacy of SIRTURO(TM) for the treatment of drug-sensitive TB has not been established. In addition, there are no data on the treatment with SIRTURO(TM) of extrapulmonary TB (e.g., central nervous system). Therefore, use of SIRTURO(TM) in these settings is not recommended.

## Important Safety Information

## **WARNINGS:**

-- An increased risk of death was seen in the SIRTURO(TM) treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO(TM) when an effective treatment regimen cannot otherwise be provided.

-- QT prolongation can occur with SIRTURO(TM). Use with drugs that prolong the QT interval may cause additive QT prolongation.

## **Warnings and Precautions**

**Increased Mortality:** An increased risk of death was seen in the SIRTURO(TM) treatment group. The imbalance in deaths is unexplained.

**QT Prolongation:** SIRTURO(TM) prolongs the QT interval. An electrocardiogram (ECG) should be obtained before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with SIRTURO(TM). Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Discontinue SIRTURO(TM) and all other QT prolonging drugs if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of >500 ms (confirmed by repeat ECG).

The following may increase the risk for QT prolongation when patients are receiving SIRTURO(TM), and therefore ECGs should be monitored closely: 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 hypothyroidism and bradyarrhythmias; a history of uncompensated heart failure; serum calcium, magnesium, or potassium levels below the lower limits of normal.

SIRTURO(TM) has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

**Hepatic-related Adverse Drug Reactions:** More hepatic-related adverse drug reactions were reported with the use of SIRTURO(TM) plus other drugs to treat TB compared to other drugs used to treat TB without the addition of SIRTURO(TM). Alcohol and other hepatotoxic drugs should be avoided while on SIRTURO(TM), especially in patients with diminished hepatic reserve. Monitor symptoms and liver-related laboratory tests. Discontinue SIRTURO(TM) if aminotransferase elevations are accompanied by total bilirubin elevation >2X ULN; aminotransferase elevations are >8x ULN; or aminotransferase elevations persist beyond 2 weeks.

**Drug Interactions:** Co-administration of strong systemic CYP3A4 inducers (e.g., rifamycins such as rifampin, rifapentine, and rifabutin) should be avoided. Co-administration with strong systemic CYP3A4 inhibitors for more than 14 consecutive days should be avoided. Appropriate clinical monitoring for SIRTURO(TM)-related adverse reactions is recommended.

**HIV-TB Co-infected Patients:** There are no clinical data on the combined use of antiretroviral agents and SIRTURO(TM) in HIV/MDR-TB co-infected patients, and only limited clinical data on the use in HIV/MDR-TB co-infected patients who were not receiving antiretroviral therapy.

**Treatment Failure:** SIRTURO(TM) should be administered by directly observed therapy. SIRTURO(TM) should only be administered in combination with at least 3 drugs active against the patient's TB isolate. Nonadherence to the treatment regimen could result in failure or resistance.

### **Adverse Reactions**

The most common adverse drug reactions reported in greater than or equal to 10.0% of patients treated with SIRTURO(TM) compared to the placebo treatment group were nausea (38.0% vs. 32.1%), arthralgia (32.9% vs. 22.2%), headache (27.8% vs. 12.3%), and additional adverse events reported in greater than or equal to 10.0% of patients and with a higher frequency than the placebo treatment group were hemoptysis (17.7% vs. 11.1%) and chest pain (11.4% vs. 7.4%).

Please see full Prescribing Information and Medication Guide for more details.

### **About SIRTURO(TM) (bedaquiline)**

SIRTURO(TM) was discovered by researchers at Janssen and is currently under review by three regulatory bodies including the European Medicines Agency (EU), State Food and Drug Administration (China) and Medicines Control Council (South Africa).

### **About Janssen Research & Development, LLC**

At Janssen, we are dedicated to addressing and solving some of the most important unmet medical needs of our time in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we develop innovative products, services and healthcare solutions to help people throughout the world. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit <http://www.janssenrnd.com> for more information.

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