WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

ADDENDUM

Bedaquiline 100mg tablet

15- Proposed (new/adapted) text for the WHO model formulary

**Bedaquiline**

**100 mg tablet**

**Uses:** Bedaquiline is indicated in adults (≥ 18 years) as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant Mycobacterium tuberculosis.

**Contraindications:** None known

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

*Increased Mortality* - in the Phase 2 (C208) trial where bedaquiline was administered for 24 weeks in combination with a background regimen, more deaths occurred in the bedaquiline treatment group than in the placebo group. After enrollment, 10 patients died in the bedaquiline treatment group (N = 79) compared to 2 patients in the placebo group (N = 81). One death occurred during administration of bedaquiline. The median time to death for the remaining nine patients was 344 days after last intake of bedaquiline. In the bedaquiline treatment group, the most common cause of death as reported by the investigator was tuberculosis (5 patients). The causes of death in the remaining bedaquiline patients varied. The imbalance in deaths is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, or severity of disease was observed.

*Cardiovascular safety* - during clinical trials with bedaquiline a prolongation of QTc interval was observed. An ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval. Bedaquiline treatment initiation is not recommended in patients with: heart failure, QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by
repeat ECG), or a personal or family history of congenital QT prolongation. If necessary, bedaquiline treatment initiation could be considered in these patients after a favorable benefit risk assessment and with frequent ECG monitoring.

Bedaquiline treatment must be discontinued if the patient develops: clinically significant ventricular arrhythmia, QTcF interval of > 500 ms (confirmed by repeat ECG).

An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other drugs that prolong the QT interval cannot be excluded. Caution is recommended when prescribing bedaquiline concomitantly with medications with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

Concomitant administration of bedaquiline with fluoroquinolone antibiotics that have a potential for significant QT prolongation (gatifloxacin, moxifloxacin and sparfloxacin) should be avoided.

In an open label Phase 2b trial (C209), mean increases from baseline in QTcF were larger in subjects with concomitant clofazimine use than in subjects without concomitant clofazimine use. In the event that co-administration of clofazimine with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

Hepatic safety - increases in transaminases were seen in clinical trials during administration of bedaquiline with the background regimen. Patients should be monitored during treatment. If AST exceeds 5 times the upper limit of normal then the regimen should be reviewed and bedaquiline and/or any hepatotoxic background drug should be discontinued. Other hepatotoxic drugs and alcohol should be avoided while on bedaquiline, especially in patients with diminished hepatic reserve.

Drug Interactions - CYP3A4 inducers/inhibitors

Bedaquiline is metabolized by CYP3A4 and its exposure may therefore be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4. Co-administration of bedaquiline and drugs that induce CYP3A4 may decrease bedaquiline plasma concentrations and reduce its therapeutic effect. Co-administration of bedaquiline and rifamycins (rifampin, rifapentine and rifabutin) or other potent CYP3A4 inducers used systemically should therefore be avoided. Co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions. Therefore, the combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided.

HIV-TB co-infected patients - there are no clinical data on the combined use of antiretroviral agents and bedaquiline in HIV/MDR-TB co-infected patients and only limited clinical data on the use of
bedaquiline in HIV/MDR-TB co-infected patients (n= 22) who were not receiving antiretroviral (ARV) therapy.

**Dose:**

The recommended dosage of bedaquiline for MDR-TB is:

- Weeks 1-2: 400 mg (4 tablets of 100 mg) once daily
- Weeks 3-24: 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses).

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

Bedaquiline should only be administered as part of a multidrug resistant tuberculosis (MDR-TB) regimen. It is recommended that bedaquiline is administered by directly observed therapy (DOT). MDR-TB is defined as in vitro resistance of the patient’s isolate to at least isoniazid and rifampin.

The prescribing physician should refer to national TB treatment guidelines for direction on selection and duration of use of companion drugs. Bedaquiline should only be used in combination with at least 3 drugs to which the patient’s isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, treatment may be initiated with bedaquiline in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible.

Throughout treatment with, and following the last intake of bedaquiline, patients should continue to take their companion drugs in accordance with national TB treatment guidelines and local MDR-TB treatment practice.

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