Bedaquiline-containing regimens cardiac adverse events

Introduction

Bedaquiline is an antimycobacterial drug used for the treatment of pulmonary multidrug resistant tuberculosis. Bedaquiline inhibits adenosine 5'-triphosphate (ATP) synthesis, a process that is crucial to the growth of mycobacterium and to its survival in its non-growing dormant state. Bedaquiline is recommended for the treatment of pulmonary Multidrug Resistant Tuberculosis (MDR-TB) and Rifampicin Resistant-Tuberculosis medicines (RR-TB) by world health organization. Bedaquiline is used in Botswana for management of MDR-TB and RR-TB.

WHO International Program on Drug Monitoring has published a potential safety signal of Bedaquiline associated with cardiac arrhythmia. 401 reported cases were identified and reviewed from the global data base of Bedaquiline associated with an adverse drug reaction (ADR) term 'cardiac arrythmia' including 28 with fatal outcome. In Botswana, as of 9th March 2023 there are 4 reported cases of Bedaquiline associated ADRs reported in the National Database. None of the reports are cardiac adverse events. Eventhough there are no such reports locally, there is an important need for close monitoring of patients on Bedaquiline-containing regimens for MDR-TB.

The review of the global data base of ADR reports identified a potential safety issue concerning weight-based dosing of Bedaquiline. Patients with very low body weight may be at greater risk of cardiac arrhythmia if appropriate weight-dosing is not followed. Therefore, it is necessary to collect data and analyze safety of use of Bedaquiline in patients with lower body weight and body mass index (BMI).

Information for Health care professionals

Bedaquiline prolongs the QTc interval. Therefore, electrocardiogram should be obtained before initiation of treatment and should be repeated monthly after starting treatment with Bedaquiline. Baseline serum potassium, calcium and magnesium should be obtained and if abnormal must be corrected before initiating treatment. Electrolytes must be closely monitored when QT prolongation is detected.

There is a possibility of additive or synergistic effect on QT prolongation when Bedaquiline is co-administered with other medicines that prolong QT interval such as ciprofloxacin, levofloxacin, erythromycin, ketoconazole, itraconazole. quetiapine, risperidone, and olanzapine. Healthcare professionals should be cautious when prescribing medicines with established risk of QT prolongation.

Bedaquiline should not be prescribed to patients with the following conditions unless the potential benefit outweigh the potential risk:

- Heart failure
- QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram)
- A personal or family history of congenital QT prolongation
- A history of or ongoing hypothyroidism
- A history of or ongoing bradyarrhythmia
- A history of Torsade de Pointes
- Concomitant administration of fluoroquinolone antibiotics that have a potential for significant QT prolongation (i.e., moxifloxacin and sparfloxacin).
- Hypokalemia

Where a patient develops clinically significant ventricular arrhythmia or a QTcF interval of > 500 ms (confirmed by repeat electrocardiogram) treatment should be discontinued.

BoMRA encourages healthcare professionals to advice patients or care givers to report any Adverse Drug Reactions (ADRs) or any discomfort anytime after they take Bedaquiline. Healthcare provider should report suspected ADRs to BoMRA using any of the following BoMRA platforms:

- **ADR reporting forms.** You may download the forms from the BoMRA website www.bomra.co.bw and email the completed for to reportadr@bomra.co.bw
- **E-reporting.** Follow the Primary eReporting (who-umc.org) link available on BoMRA website and complete the form online.
- **MedSafety App.** Use the ADRs reporting App, available in apple store or google store for smart phones
- **Call BoMRA** at 373 1727/ 20

For more information about any medicine/vaccine safety contact, BoMRA **National Medicines Information Centre** at 373 1788/71 or email nmic@bomra.co.bw