Suspected Adverse Drug Reactions of Angiotensin 11 converting enzyme inhibitors reported to BoMRA

INTRODUCTION

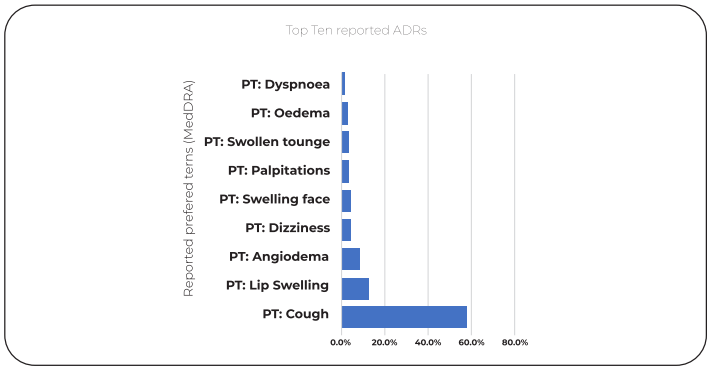
Botswana Medicines Regulatory Authority (BoMRA) continues to monitor safety of medicinal products registered in Botswana. One of the key activities is to advocate for adverse drug reactions (ADRs) reporting, assessment, and analysis. BoMRA has analyzed safety reports associated with angiotensin converting enzyme inhibitors (ACEIs) received between 1st April 2019 and 28th February 2023.

ACEIs are commonly used in the management of hypertension, heart failure, post myocardial infarction care, and to slow progression of renal disease associated with diabetes. ACE inhibitors block an angiotensin-converting enzyme that converts angiotensin I to angiotensin II. Decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodelling of smooth muscle and cardiac myocytes.

ADR analytics

As of 28th February 2023, BoMRA has received 122 individual case safety report (ICSRs). Majority of the reports received were observed in females (66.4%). Patients aged between 45-64 years experienced more ADRs (39.3%) followed by age group 65-74 years (22.1%). The most affected system is respiratory, thoracic, and mediastinal disorders at 59.0%, followed by gastrointestinal system and least affected is the musculoskeletal and connective tissue disorders at 0.8%. Four topmost common co-reported medicines are metformin, hydrochlorothiazide, nifedipine and atorvastatin at 22.1%, 15.6%, 13.9% and 10.7% respectively.

Figure 1: Top 10 reported ADRs



The most common reported ADRs are cough (57.4%), lip swelling (12.3%), angioedema (8.2%), dizziness and swelling face both at (4.1%) (see figure 1). These are all known ADRs associated with ACEIs, and they are well characterized and included in both the patient information leaflet and summary of product characteristics. Of all the cases only 23.8% were classified as serious and 75.4% are non-serious. The data received at BoMRA is consistent with the global data. The reports came from nurses 45.9%, pharmacists 45.9% and doctors 7.4% (see figure 2). The data received in Botswana is consistent with global data.

Angioedema and Lip swelling

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients taking ACE inhibitors, including enalapril. Angioedema may occur at any time during treatment; may occur more frequently in patients of Black African origin than in non-black patients. Enalapril should be promptly discontinued, and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms occur. Laryngeal oedema may be fatal, in cases with involvement of the tongue, glottis or larynx, appropriate therapy should be initiated immediately. Angioedema has been reported in clinical trials at 0.5% to 1% in patients taking enalapril compared to those taking placebo or compactor drugs. The incidence rate in clinical trials is similar to incidence rate reported in post-marketing surveillance.

Post Authorization Studies have reported dry cough in 1.3% hypertensive patients and 2.2% of congestive heart failure patients treated with enalapril compared to 0.9% and 0.6% of patients who received placebo for the hypertensive and heart failure patients.

Figure 2: Reporters by qualifications

Reporter qualification	Percentage
Physician	7.4%
Pharmacist	45.9%
Nurses	45.9%
Consumer/Non-Health Professional	0.8%

Mechanism of action for both angioedema and dry cough is currently unknown; however, it has been suggested that bradykinin might be responsible for angioedema and dry cough in patients. Angiotensin converting enzyme (ACE) is identical to kininase. As a result, ACE inhibition may block bradykinin metabolism resulting in more severe angioedema and dry cough.

Predisposing risk factors

Angioedema and dry cough are not dose and duration dependent. Clinical trials and post marking experience have shown that people of Chinese, Japanese, Indian, and African origin appear to be more susceptible. Further, females are 2 to 3 times more susceptible than males and elderly patients are at higher risk.

Practice points to healthcare professionals

Angioedema and dry cough resolve few days after discontinuation of the ACEIs. Further rechallenge with another ACE inhibitor usually results in recurrence in most patients, and cross- occurrence when patients take other AECIs is well documented. Health care professionals are advised to monitor any adverse drug reactions or discomfort reported by patients after treatment with ACEIs. 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