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RWANDA FDA
Rwanda Food and Drugs Authority
P.O. Box 84 Kigali
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Dear Healthcare professionals

Re: New safety information regarding Hydrochlorothiazide association with non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)

Dear Sir/Madam,

The role of Rwanda FDA is to protect the public health by disseminating information on quality and safety of products regulated under the Law No 003/2018 of 09/02/2018 to health professionals and general public. Rwanda FDA also has the mandate to follow up and analyzes information on the use of medical products that are subject to global drugs safety monitoring.

In this regard, Rwanda FDA has analyzed the information received from Marketing Authorization Holder (AstraZeneca) in agreement with European Medicines Agency (EMA), Pharmacovigilance Risk Assessment Committee (PRAC) on the association of Hydrochlorothiazide and non-melanoma skin cancer (NMSC); therefore, Rwanda FDA would like to inform Healthcare professionals the following:

Summary

- Pharmaco-epidemiological studies have reported an association of non-melanoma skin cancer (NMSC; i.e basal cell carcinoma, squamous cell carcinoma) with exposure to hydrochlorothiazide (HCTZ)-containing medicines.
- Patient taking hydrochlorothiazide alone or in combination with other medications should be informed of the association of non-melanoma skin cancer NMSC with the use of Hydrochlorothiazide HCTZ containing medicines and advised to regularly check their skin for any new lesions as well as changes to existing ones and report any suspicious skin lesions.

- Suspicious skin lesions should be examined potentially including histological examinations of biopsies.
- Patients should be advised to limit exposure to sunlight and UV rays and use adequate protection when exposed to sunlight and UV rays.
- The use of HCTZ may also need to be carefully reconsidered in patients who have had previous skin cancer.

For Safety Reasons, Rwanda FDA has requested manufacturers and distributors to include in pack sizes of HCTZ formulations marketed in Rwanda, the revised Patient Information Leaflet (PIL) containing above warnings and precautions.

Reporting any suspected adverse event is important for the continued monitoring of the safety of all medicines. Any adverse events which are experienced with this medicine should be reported by healthcare professionals and/or patients to the Rwanda FDA via e-mail: info@rwandafda.gov.rw

Please forward this information to relevant staff members in your institution/catchment area.
Kindly find attached herewith the summary of study's findings

Sincerely,

Dr KARANGWA Charles
Ag. Director General of Rwanda FDA

CC:

- **Hon. Minister of Health**
- **Hon. Minister of State in Charge of Primary Health Care**
- **Director General of RBC**
- **Director General of Referral Hospital (All)**
- **Director General of Provincial Hospital (All)**
- **Director General of District Hospital (All)**
- **Private Hospital and Clinic (All)**

Background on the Safety concern

HCTZ containing medicinal products are widely used to treat hypertension, as well as cardiac, hepatic and nephrogenic oedema or chronic heart insufficiency.

AstraZeneca has assessed the cumulative available data from all relevant sources. Two recent pharmaco-epidemiological studies conducted in Danish nationwide data sources (including Danish Cancer Registry and National Prescription Registry) have reported a cumulative dose-dependent association between HCTZ and NMSC (i.e basal cell carcinoma, squamous cell carcinoma. Photosensitizing actions of HCTZ could act as possible mechanism for NMSC.

One study[1] included population comprised of 71,533 cases of basal cell carcinoma (BCC) and 8,629 cases of squamous cell carcinoma (SCC) matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥ 50,000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1.29 (95% confidence interval (CI): 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A cumulative dose response relationship was observed for both BCC and SCC.
For example, 50,000 mg cumulative dose corresponds to 12.5 mg HCTZ taken daily for about 11 years.

Another study [2] reported a possible association between lip-cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer (SCC) were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was reported with adjusted OR 2.1(95% CI: 1.7-2.6) for ever users increasing to OR 3.9 (3.0-4.9) for high use (25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (100,000mg).

NMSC is a rare event. Incidence rates highly depend on skin phenotypes and other factors leading to different baseline risks and varying incidence rates in different countries. Estimated incidence rates vary across different regions in Europe and are estimated at rates of around 1 to 34 cases per 100,000 inhabitants per year for SCC and 30 to 150 per 100,000 inhabitants per year BCC.

Based on this assessment, the prescribing information for all the AstraZenaca HCTZ containing products will be updated to include a warning on the association of NMSC with the use of HCTZ. Also, the European Medicines Agency (EMA) has recently recommended the marketing authorization holders of HCTZ containing products to update EU SmPCs on the topic of NMSC and HCTZ.

References

1. Pedersen et al., Hydrochlorothiazide use and risk of non melanoma skin cancer: A nationwide case-control study from Denmark.J Am Acad Dermatol 2018; 78:673-681

2. Pottegard A, Hallas J,OlesenM,Svendsen MT, Habel LA, Friedman GD, Friis S. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med 2017; 282: