DRUG SAFETY INFORMATION No.65

23 July 2019

Health Products Regulation Group
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Dear Healthcare Professional

RISK OF NON-MELANOMA SKIN CANCER ASSOCIATED WITH USE OF HYDROCHLOROTHIAZIDE

The Health Sciences Authority (HSA), in consultation with its Product Vigilance Advisory Committee (PVAC), would like to update healthcare professionals on the outcome of its review regarding the risk of non-melanoma skin cancer (NMSC) associated with hydrochlorothiazide (HCTZ) use. Two recent Danish epidemiological studies had suggested a cumulative dose-dependent association between its use and NMSC. HSA's review concluded that while the Danish studies may not be fully applicable to the local context, there is biological plausibility of patients developing NMSC due to the photosensitizing effects of HCTZ. Hence, healthcare professionals are advised to consider the possible risk of NMSC in the use of HCTZ in their patients.

Background

2 HCTZ is a thiazide diuretic that is used in treatment of hypertension. It is available either as a single ingredient or in combination with other anti-hypertensive agent/s.

3 NMSC, which consists mainly of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is the most common type of skin cancer globally. From 2011 to 2015, the incidence rates of skin cancer in Singapore men and women were 19.3 and 14.4 per 100,000 person-years, respectively.[1] The known risk factors for NMSC include, but are not limited to UV exposure, immunosuppression, photosensitising medications, and fair or light skin complexion. The possible mechanism of NMSC attributed by HCTZ has been postulated to be due to its photosensitizing properties which may influence cancer risk at sun-exposed sites and may also induce a chronic inflammatory reaction.

4 Two recent pharmacoepidemiological studies using data from the Danish registries had found a cumulative dose-dependent association between HCTZ use and NMSC.

5 One study included 71,533 patients with BCC and 8,629 patients with SCC, who were matched with population controls in a 1:20 ratio by age and sex.[2] High cumulative usage of HCTZ (i.e. ≥50 g, corresponding to 12.5 mg daily for about 11 years) was found to be associated with an increased risk of BCC (adjusted odds ratio [OR]=1.29; 95% CI=1.23-1.35) and SCC (OR=3.98; 95% CI=3.68-4.31). A dose-response pattern was observed in this study for both BCC and SCC, with a more than seven-fold increased risk of SCC for cumulative use of ≥200 g HCTZ (BCC: OR=1.54; 95% CI=1.38-1.71; SCC: OR=7.38; 95% CI=6.32-8.60).

6 In another Danish study, which included 633 cases with SCC of the lip, matched with 63,067 population controls,[3] a cumulative dose-response relationship between the use of HCTZ and SCC of the lip was also demonstrated. The adjusted OR with ever-use of HCTZ for SCC lip cancer was 2.1 (95% CI=1.7-2.6), which increased to 3.9 (95% CI=3.0-4.9) and 7.7 (95%CI=5.7-10.5) with high cumulative HCTZ use of ≥25 g and ≥100 g, respectively.

International Regulatory Actions

7 International regulatory health authorities, namely, the European Medicines Agency (EMA)[4], Health Canada[5] and New Zealand Medsafe[6] have requested for the package inserts (PIs) of HCTZ-containing products to be updated with warnings on NMSC. EMA and Health Canada have also issued communications to healthcare professionals to highlight this risk and the preventive measures to be considered for patients to minimise the risk of skin cancer.

Expert consultations with Chapters of Academy of Medicine

8. Expert advice was sought from three Chapters from the Academy of Medicine, Singapore, namely: i) Chapter of Dermatologists, ii) Chapter of General Physicians, iii) Chapter of Medical Oncologists regarding this safety issue. Their overall sentiment was that the findings from the Danish epidemiological studies may not be fully applicable to the local context due to different baseline skin cancer risks between the Danish and Singapore populations. Danes have lighter skin phototypes that are known to have a higher susceptibility to skin cancer. The skin phototypes of the Singapore population are darker and skin cancer incidence in Singapore is lower than in the Danish studies. None of the Chapters had encountered cases of NMSC associated with the use of HCTZ.

HSA's Benefit-risk Assessment and Advisory

9 HSA's assessment took into consideration findings from scientific literature, expert opinions of the local dermatologists, medical oncologists and general physicians as well as regulatory actions taken by the international regulatory health authorities.

10 HSA has assessed that the findings from the two Danish epidemiological studies may not be fully applicable to the local context due to different baseline skin cancer risks (e.g. different skin phototypes) between the Danish and the Singapore populations. The Danes are of northern European origin and typically have lighter skin phototypes with higher susceptibility of sunburn and skin cancers while the Singaporean population typically have darker skin phototypes. In addition, sun exposure which is an important risk factor for skin cancer was not accounted for in the studies. To date, HSA has not received any local reports of NMSC suspected to be associated with the use of HCTZ. However, considering the biological plausibility of patients developing NMSC due to the photosensitizing effects of HCTZ, HSA would like to advise healthcare professionals of the following:

- To inform patients taking HCTZ alone, or combination drugs containing HCTZ of the potential risk of NMSC.
- To advise patients on HCTZ to regularly check their skin for any new lesions or changes to existing ones, and promptly report any suspicious skin lesions to their doctor.
- To counsel patients on possible preventive measures such as to limit exposure to sunlight and UV rays and to use adequate sun protection to minimise the risk of skin cancer.
- For patients with history of skin cancer or with high risk of skin cancer (e.g. light-coloured skin, immunosuppression), the use of HCTZ may need to be reconsidered.

11 HSA is working with the companies to strengthen the local PIs of HCTZ-containing products to warn of the potential risk of NMSC. HSA will also continue to closely monitor the international and local developments of this issue and update healthcare professionals of any new significant findings.

12 Healthcare professionals are encouraged to report any suspected serious adverse events related to use of HCTZ to the Vigilance and Compliance Branch at Tel: 6866 1111, Fax: 6478 9069, or report online at http://www.hsa.gov.sg/ae_online. Should you have further queries regarding this matter, please contact Ms Liesbet Tan at Tel: 6304 5464 or email: liesbet_tan_from.tp@hsa.gov.sg.

Thank you.

Yours faithfully

MS JALENE POH
DIRECTOR
VIGILANCE AND COMPLIANCE BRANCH
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health
Chief Executive Officer, Health Sciences Authority

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