

**South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Cardiovascular conditions**

SUMMARY REVIEW

Date: 6 December 2018

Hydrochlorothiazide and skin cancer

Background

Letter, dated 7 November 2018 was circulated by certain suppliers (in collaboration with the South African Health Products Regulatory Authority) of hydrochlorothiazide (HCTZ) to Healthcare Professionals informing of the risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) with hydrochlorothiazide¹. Product labels will be updated accordingly. Consequently, a number of concerns were received from Provinces and this summary provides an overview of the risk.

Evidence overview

Hydrochlorothiazide (HCTZ) is associated with phototoxic and photo allergic skin reactions as well as drug-induced lupus². A case-control study using the Danish Cancer Registry (2004-2012)³ observed 71533 cases of basal cell carcinoma (BCC) and 8629 cases of squamous cell carcinoma (SCC) in those exposed to hydrochlorothiazide (HCTZ) diuretics. The cases were cross-referenced with the Danish National Prescription Registry to determine cumulative HCTZ exposure. The cases were compared with 172 000 population controls.

The proportion of skin cancers attributable to HCTZ use was 9% for SCC and 0.6% for BCC. HCTZ ($\geq 50,000$ mg) use increased the odds of BCC and SCC by 1.29 (95% confidence interval [CI], 1.23 to 1.35) and 3.98 (95% CI, 3.68 to 4.31), respectively.

A dose-response relationship between HCTZ use and both BCC and SCC was found. The highest cumulative dose category ($\geq 200,000$ mg of HCTZ) had an OR of 1.54 (95% CI, 1.38-1.71) and 7.38 (95% CI, 6.32-8.60) for BCC and SCC, respectively.

Whilst the findings of the study are concerning, the study design limits the generalisability of the findings e.g. no information on sun exposure was available; the period of time of HCTZ administration was not provided to determine the daily dose and the study cohort were Danish patients of fair complexion .

Previously, case-control study of Danish nationwide registry data reported an association between HCTZ and squamous cell carcinoma (SCC) of the lip⁴. Adjusted OR for SCC lip cancer was 2.1 (95% CI 1.7 to 2.6), increasing to 3.9 (95% CI 3.0 to 4.9) for high use ($\geq 25,000$ mg) and 7.7 (95%CI 5.7 to 10.5) with the highest cumulative dose ($\geq 100,000$ mg). However, the study did not adjust for tobacco smoking and should be interpreted with caution.

The evidence is limited and until further studies are available, it is recommended that those taking HCTZ should be screened for SCC and BCC.

¹ Ranbaxy (S.A.) (Pty) Ltd; Roche Products (Pty) Ltd; Sanofi-Aventis South Africa (Pty) Ltd. Dear HCP letter: Hydrochlorothiazide: risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma), 7 November 2018.

² South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

³ Pedersen SA, Gaist D, Schmidt SA, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. *J Am Acad Dermatol* 2018;78:673-681.

⁴ Pottegård A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med*. 2017;282:322-331.

Education on sun avoidance and sun protection may be appropriate for those exposed to hydrochlorothiazide.

Pharmacovigilance reports

The South African Health Products Regulatory Authority (SAHPRA) have to date, received no adverse drug reports (ADRs) of carcinoma associated with use of HCTZ⁵. Furthermore, the World Health Organisation (WHO) Uppsala Monitoring Centre has limited individual case safety reports (ICSRs) of HCTZ associated with carcinoma within the Vigibase database⁶. Table 1, below lists the respective ICSRs for HCTZ, with overall majority of ICSRs received from the Americas, Europe and Asia.

| Individual case safety reports of HCTZ | Number of reports (%) |
|--|-----------------------|
| Photosensitivity | 451 (2.21%) |
| Basal cell carcinoma | 12 (0.06%) |
| Skin cancer | 7 (0.03%) |
| Squamous cell carcinoma | 7 (0.03%) |
| Squamous cell carcinoma of skin | 4 (0.02%) |
| Total number of ICSRs for HCTZ | 20442 |

Table 1: Individual case safety reports of hydrochlorothiazide reports extracted from Vigibase (1968 to 25-Nov-2018).

Recommendation: The Adult Hospital Level Committee recommends that:

- HCTZ be retained in the national Essential medicines List; and that patients taking HCTZ be screened for SCC and BCC.
- Education on sun avoidance and sun protection may be appropriate for those exposed to hydrochlorothiazide.
- If feasible, those with a history of skin cancer and/or risk factors (light skin, immunosuppression, strong family history of skin cancer) should be offered an alternative antihypertensive agent.
- Any change of medication as per indication should be reported for pharmacovigilance surveillance.
- Furthermore, communication (circular from NDoH) should be provided to healthcare workers providing information in local context; and a caution be included in the respective STGs.
- Of importance is that management of blood pressure is a package of care and lowering blood pressure results in a reduction of cardiovascular events. Healthcare workers should be cautioned about switching treatment in patients whose BP is adequately controlled on hydrochlorothiazide.

Rationale: Limited evidence suggests a possible risk of skin cancer associated with hydrochlorothiazide. However, the evidence is not sufficient to warrant removal of HCTZ from the National EML; but a caution of photosensitivity due to HCTZ should be provided and the possible risk of skin cancer with HCTZ (through updating of STGs and dissemination of a circular).

⁵ SAHPRA communication on file (e-mail), dated 23 November 2018.

⁶ WHO Vigibase. [Internet] [Accessed 25 November 2018] Available at: <http://www.vigiaccess.org/>