health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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Reference: EDP032019/02

UPDATED NOTICE: RISK OF SKIN CANCER ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Note: The previous circular: "***Notice:*** *Risk of skin cancer associated with hydrochlorothiazide",* reference EDP122018/04 that was disseminated in December 2018 is replaced with this updated circular (reference: EDP032019/02).

Hydrochlorothiazide (HCTZ) is listed on the National Essential Medicines List for the first-line management of congestive cardiac failure, hypertension, myocarditis, stroke and neurological disorders.[1] HCTZ is associated with the uncommon occurrence of phototoxic and photo allergic skin reactions as well as drug-induced lupus.[2]

Recently, medicine safety information was provided to Healthcare Professionals by certain suppliers (in collaboration with the South African Health Products Regulatory Authority) regarding the possible risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) in patients treated with HCTZ for prolonged periods.

Note: Management of blood pressure is important in reducing cardiovascular events. Healthcare workers should be cautioned against switching treatment in patients whose blood pressure is adequately controlled on HCTZ or combination therapy with HCTZ[3].

Studies:
Observations from case control studies using Danish Registry data suggests that accumulative HCTZ exposure may increase the risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). A dose-response relationship between HCTZ use and both BCC and SCC was found. Whilst the findings of the studies are concerning, the study design limits the generalisability of the findings: no information on sun exposure was available; the study cohort were Danish patients of fair complexion and the study did not adjust for tobacco smoking. The dose response relationship showed that high HCTZ utilisation (>50 000mg cumulative exposure) was associated with an adjusted odds ratio of 1.29 for BCC and 3.98 for SCC. A cumulative exposure of 50 000 mg is equivalent to taking 12.5 mg of HCTZ daily for approximately 11 years.

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 HCTZ.[4] Furthermore, the World

[1] PHC STGs and EML, 2018; Adult Hospital Level STGs and EML, 2015; Paediatric Hospital Level STGs and EML, 2017 http://www.health.gov.za/
[2] South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
[3] Wright JM, Musini VM, Gill R. First-line drugs for hypertension. Cochrane Database Syst Rev. 2018 Apr 18;4:CD001841. https://www.ncbi.nlm.nih.gov/pubmed/29667175
[4] SAHPRA ccommunication on file (e-mail), dated 23 November 2018.

Health Organization (WHO) Uppsala Monitoring Centre has limited individual case safety reports (ICSRs) of HCTZ associated with carcinoma within the Vigibase database.[5]

Recommendations:

- HCTZ will be retained on the National Essential Medicines List for the management of congestive cardiac failure, hypertension, myocarditis, stroke and neurological disorders.
- *Patients on HCTZ*: Do not switch medication, continue HCTZ therapy, and screen for SCC and BCC in patients at high risk of skin cancer.
- *Patients initiating HCTZ*: Risk assess patients prior to starting HCTZ – patients with a history or family history of skin cancer should be offered an alternative therapeutic agent (consult doctor/specialist if required).
- Counsel patients exposed to HCTZ on sun avoidance and sun protection.

Provinces and Health Care Facilities are requested to distribute and communicate this information in consultation with the Pharmacy and Therapeutics Committees.

Comments may be submitted via e-mail or post to:

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Kind regards

K Jamaloodien

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DATE: 6/3/2019

[5] WHO Vigibase. [Internet] [Accessed 25 November 2018] Available at: http://www.vigiaccess.org/
- For the period 1968 to 25 Nov 02018, the number of reports: *Basal cell carcinoma 0.06; Skin cancer 0.03%; Squamous cell carcinoma (0.03%); Squamous cell carcinoma of skin (0.02%).*