

24-Aug-2020

Direct Healthcare Professional Communication

Hydrochlorothiazide - Association with non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)

Dear Healthcare Professional,

AstraZeneca in agreement with the Saudi Food and Drug Authority -SFDA- would like to inform you of 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.
- Patients taking HCTZ alone or in combination with other medications should be informed of the association of NMSC with the use of 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.

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 ($\geq 50,000$ 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 (~100,000 mg).

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 for BCC.

Based on this assessment, the prescribing information for all the AstraZeneca 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.

Call for reporting

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

The National Pharmacovigilance and Drug Safety Centre NPC:

Email: npc.drug@sFDA.gov.sa

Fax: +966112057662

Toll free phone: 19999

Or by online: <https://ade.sFDA.gov.sa>

Pharmacovigilance department in AstraZeneca, Saudi Arabia:

Call AstraZeneca at +966112249235

Email to Ksa.ae@astrazeneca.com

References:

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

[2] Pottgard A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; 282: 322–331.