

12th december 2018

Subject: Hydrochlorothiazide containing products – Safety communication

Hydrochlorothiazide - Risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)

Dear Healthcare Professional,

Laboratorios CINFA, S.A. as marketing authorisation holder of the products containing hydrochlorothiazide in agreement with the Ministry of Health in Kuwait would like to inform you of the following:

Summary

- Pharmacoepidemiological studies have shown an increased risk of non-melanoma skin cancer (NMSC) (basal cell carcinoma, squamous cell carcinoma) with exposure to increasing cumulative doses of hydrochlorothiazide (HCTZ)
- Patients taking HCTZ alone or in combination with other medications should be informed of the risk of NMSC 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 to minimize the risk of skin cancer.
- 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.

EMA Pharmacovigilance Risk Assessment Committee (PRAC) assessed the available data sources (i.e. literature, EudraVigilance). Two recent pharmaco-epidemiological studies conducted in Danish nationwide data sources (including Danish Cancer Registry and National Prescription Registry) have shown a cumulative dose-dependent association between HCTZ and NMSC (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] showed 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 demonstrated 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 the results of the two Danish epidemiological studies, this risk might increase approx. 4 to 7.7-fold for SCC and 1.3-fold for BCC depending on the cumulative dose of HCTZ.

The Summary of Product Characteristics and Package Leaflet for all the concerned products will be updated to inform on the risk of NMSC associated with the use of HCTZ.

Call for reporting

As a reminder, there is a need to report any suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Company contact points

If you have any questions or require further information about our hydrochlorothiazide containing products, please contact the Pharmacovigilance Department at Laboratorios Cinfa on farmacovigilancia@cinfa.com or contact our Local Agent in Kuwait (<http://aaw.com/contact-us/>).

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] Pottegard 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.

Faithfully,

A handwritten signature in blue ink that reads "Olga Mariscal". The signature is written over a faint, light blue background that contains the word "cinfa" in a stylized font.

Olga Mariscal Fernández, MD
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