IMPORTANT MEDICINES SAFETY INFORMATION

06 September 2021
Ref no. 507-2021.09.06-NN

Dear Healthcare Professional,

RE: HYDROCHLOROTHIAZIDE – RISK OF NON MELANOMA SKIN CANCER (BASAL CELL CARCINOMA, SQUAMOUS CELL CARCINOMA)

In agreement with Botswana Medicines Regulatory Authority,(BOMRA) Sanofi would like to inform you of the following about HCTZ-containing products:

Summary

- Pharmacoepidemiological studies in Danish populations have shown an increased risk of non-melanoma skin and lip cancer (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 non-melanoma skin and lip cancer 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 ultraviolet rays and use adequate protection when exposed to sunlight and UV rays to minimize the risk of skin cancer.
- The use of HCTZ-containing products may also need to be carefully reconsidered in patients who have had previous skin and lip 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, and other approved indications.

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 1,430,883 and 172,462 population controls, respectively. High HCTZ use (≥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 clear cumulative dose-response relationship was observed for both BCC and SCC.

Another study [2] showed a possible association between risk of lip-cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer (SCC) were matched with 63,067 population controls. A clear cumulative dose-response relationship was demonstrated with adjusted OR 2.1 (95% CI: 1.7-2.6) for ever-user, OR 3.9 (3.0-4.9) for high use (at least 25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (at least 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 local labelling as well as any applicable patient leaflet for CO Irberwin 150/12,5mg & CO Irberwin 300/12,5mg and all the concerned Sanofi products will be updated to inform on the risk of NMSC associated with the use of HCTZ-containing products.

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 (ADR) via the ADR reporting form https://www.bomra.co.bw/index.php/adr-reporting on the BoMRA website (www.bomra.org.bw)

Table 1 : Hydrochlorothiazide- containing medicines

Company	**Product Name**	**Active Ingredients**	**Reference Number**	**Contact Details**
Sanofi-Aventis South Africa (Pty) Ltd	CO-IRBEWIN 300 mg tablets	Hydrochlorothiazide 12,5 mg + Irbesartan 300 mg)	BOT1803315	*Tel:* +27 11 256 3700 *Email:* za.drugsafety@ sanofi.com
	CO-APPROVEL 150 /12,5 mg tablets	Hydrochlorothiazide 12,5 mg + Irbesartan 150 mg)	BOT1001637A BOT1001637B	
	CO-APPROVEL 300 mg/12,5 mg	Hydrochlorothiazide 12,5 mg + Irbesartan 300 mg)	BOT0801229	

Yours faithfully

GRAEME JAMES

Responsible Pharmacist

Sanofi-Aventis South Africa

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: