

October 2018

Direct Healthcare Professional Communication

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

Dear

Following a European safety review, Marketing Authorisation Holders of medicines containing hydrochlorothiazide, in agreement with the Medicines and Healthcare Products Regulatory Agency (MHRA), would like to inform you of the following new safety information:

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**
- **Patients taking medicines containing hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check for and report any new or changed skin lesions or moles**
- **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 minimise the risk of skin cancer**
- **The use of hydrochlorothiazide may also need to be carefully reconsidered in patients who have had previous skin cancer**

Background on the safety concern

Hydrochlorothiazide-containing medicinal products are used to treat hypertension, as well as cardiac and hepatic oedema, or chronic heart insufficiency.

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) assessed the available data sources. Two recent pharmacoepidemiological studies of Danish nationwide data sources (including the Danish Cancer Registry and National Prescription Registry) have shown a cumulative dose-dependent association between hydrochlorothiazide and NMSC (basal cell carcinoma, squamous cell carcinoma). Photosensitising actions of hydrochlorothiazide could act as the possible mechanism for NMSC.

One study [1] included a population 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 hydrochlorothiazide 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, a cumulative dose of 50,000 mg corresponds to 12.5 mg hydrochlorothiazide taken daily for about 11 years.

Another study [2] showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 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 an 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 ($\geq 25,000$ mg) and OR 7.7 (5.7–10.5) for the highest cumulative dose ($\geq 100,000$ 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 approximately 4 to 7.7-fold for SCC and 1.3-fold for BCC depending on the cumulative dose of hydrochlorothiazide.

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

Call for reporting

Suspected adverse drug reactions (ADRs) should be reported to the MHRA through the Yellow Card Scheme. When reporting, please provide as much information as possible.

It is easiest and quickest to report ADRs online via the Yellow Card website:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary), by emailing yellowcard@mhra.gov.uk, at the back of the British National Formulary (BNF), by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789, or by downloading and printing a form from the Yellow Card section of the MHRA website.

Yours sincerely,



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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.

Company contact details

These materials are being sent to you on behalf of the group of companies listed below, who are Marketing Authorisation holders for medicines containing hydrochlorothiazide. If you require additional information, please contact the medical information services of the individual company.

Company	Medical Information contact details
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Bayer plc	Email: medical.information@bayer.co.uk Telephone: 0118 206 3116
Boehringer Ingelheim Limited	Email: medinfo.bra@boehringer-ingelheim.com Telephone: 01344 742 579
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Generics (UK) Ltd t/a Mylan	Email: info.uk@mylan.co.uk Telephone: 01748 828 888
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Teva and Teva Group entities	Email: medinfo@tevauk.com Telephone: 0207 540 7117
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