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Direct Healthcare Professional Communication

Hydrochlorothiazide - Risk of non-melanoma skin cancer

(basal cell carcinoma, squamous cell carcinoma)

Dear **Healthcare Professional,**

A. Menarini International Operations S.A., Actavis International Limited, AstraZeneca UK Ltd, Aurobindo Pharma (Malta) Ltd, Boehringer Ingelheim International GmbH, Generics [UK] Limited, Mylan IRE Healthcare Limited, NeoFarma Pharmaceuticals Ltd, Novartis Europharm Limited, Novartis Ireland Limited, Remedica Ltd, Teva B.V and Wockhardt UK Limited, marketing authorisation holders of the products containing hydrochlorothiazide in agreement with the European Medicines Agency and the Malta Medicines Authority 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 (≥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

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with hydrochlorothiazide medicines in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

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 points

Company	Product name	Email	Phone
A. Menarini International Operations S.A.	Omesar Plus 20/12.5mg Omesar Plus 20/25mg	rp2@ammangion.com	+356 2397 6412
Actavis International Limited	Actelsar HCT	PHVMALTA@actavis.com	+30 2118805166
Astrazeneca UK Ltd	Atacand Plus 16/12.5mg Tablets Zestoretic 20mg/12.5mg Tablets	Alexia.farrugia@astrazeneca.com	+356 22778115
Aurobindo Pharma (Malta) Ltd	Fosinopril + Hydrochlorothiazide Aurobindo 20mg + 12.5mg, Tablets Losartan/Hydrochlorothiazide Glob Limited 50mg/12.5mg film-coated Tablets Losartan/Hydrochlorothiazide Glob Limited 100mg/12.5mg film-coated Tablets Losartan/Hydrochlorothiazide Glob Limited 100mg/25mg film-coated Tablets Valsartan and Hydrochlorothiazide 80mg/12.5mg film-coated Tablets Valsartan and Hydrochlorothiazide 160mg/12.5mg film-coated Tablets Valsartan and Hydrochlorothiazide 160mg/25mg film-coated Tablets Valsartan and Hydrochlorothiazide 320mg/12.5mg film-coated Tablets Valsartan and Hydrochlorothiazide 320mg/25mg film-coated Tablets Irbesartan/ Hydrochlorothiazide Aurobindo 150mg/12.5mg film-coated Tablets Irbesartan/ Hydrochlorothiazide Aurobindo 300mg/12.5mg film-coated Tablets Irbesartan/ Hydrochlorothiazide Aurobindo 300mg/25mg film-coated Tablets Candesartan/Hydrochlorothiazide 8mg/12.5mg Tablets Candesartan/Hydrochlorothiazide 16mg/12.5mg Tablets Candesartan/Hydrochlorothiazide 32mg/12.5mg Tablets Candesartan/Hydrochlorothiazide 32mg/25mg Tablets Olmesartan/Hydrochlorothiazide Tablet, film coated 20mg/12.5mg Olmesartan/Hydrochlorothiazide Tablet, film coated 20mg/25mg Olmesartan/Hydrochlorothiazide Tablet, film coated 40mg/12.5mg Olmesartan/Hydrochlorothiazide Tablet, film coated 40mg/25mg Quinapril/Hydrochlorothiazide 10/12.5mg Film-coated tablets Quinapril/ Hydrochlorothiazide 20mg/12.5mg Film-coated tablets Quinapril/ Hydrochlorothiazide 20mg/25mg Film-coated tablets	Pharmacovigilance.Malta@ aurobindo.com	+356 22294163
Boehringer Ingelheim International GmbH	MicardisPlus 40mg/12.5mg Tablets MicardisPlus 80mg/12.5mg Tablets MicardisPlus 80mg/25mg Tablets	Medinfo.bra@boehringer-ingelheim.com	+44 1344 742579
Generics [UK] Limited	Bisocombimyl 2.5mg/6.25mg film-coated tablet Bisocombimyl 5mg/6.25mg film-coated tablet Bisocombimyl 10mg/6.25mg film-coated tablet Cobisomyl 5mg/12.5mg film-coated Tablets Cobisomyl 10mg/25mg film-coated Tablets	Info.uk@mylan.co.uk	+ 44 1748 828888

Company	Product name	Email	Phone
	Bisoprohydrochlor 2.5mg/6.25mg film-coated tablet Bisoprohydrochlor 5mg/6.25mg film-coated tablet Bisoprohydrochlor 10mg/6.25mg film-coated tablet Lisinogen Combi 20mg/12.5mg Tablet Co-Lisinomyl 10mg/12.5mg Tablet Co-Lisinomyl 20mg/12.5mg Tablet Lisinopril/Hydrochlorothiazide Mylan 20mg/12.5mg Tablet		
Mylan IRE Healthcare Limited	Teveten Plus 600mg/12.5mg, film coated Tablets	Info.uk@mylan.co.uk	+ 44 1748 828888
Neofarma Pharmaceuticals Ltd	Atacand Plus Co Diovan	Info@neofarma.com.mt Rp@neofarma.com.mt	+356 20109494
Novartis Europharm Limited	Copalia HCT Dafiro HCT Exforge HCT	Novartis.malta@novartis.com Drug_safety.malta@novartis.com	+356 2122 2872
Novartis Ireland Limited	Co-Diovan Tablet, film coated 320mg/12.5mg Co-Diovan Tablet, film coated 320mg/25mg Co-Diovan Tablet, film coated 80mg/12.5mg Co-Diovan Tablet, film coated 160mg/12.5mg Co-Diovan Tablet, film coated 160mg/25mg	Novartis.malta@novartis.com Drug_safety.malta@novartis.com	+356 2122 2872
Remedica Ltd	Milorex tablets	A.Vasiliou@remedica.com.cy	+357 25 55 32 51
Teva B.V.	Irbesartan/Hydrochlorothiazide Teva	PHVMALTA@actavis.com	+30 2118805166
Wockhardt UK Limited	Co-amilozide 5/50 Tablets	Drug.safety@wockhardt.co.uk	+44(0) 1978 669 272

Yours faithfully,

Post-Licensing Directorate
Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of A. Menarini International Operations S.A., Actavis International Limited, Astrazeneca UK Ltd, Aurobindo Pharma (Malta) Ltd, Boehringer Ingelheim International GmbH, Generics [UK] Limited, Mylan IRE Healthcare Limited, Neofarma Pharmaceuticals Ltd, Novartis Europharm Limited, Novartis Ireland Limited, Remedica Ltd, Teva B.V., Wockhardt UK Limited together with their local representatives.