



IMPORTANT MEDICINE SAFETY INFORMATION

26 October 2018

Dear Healthcare Professional

Re:

HYDROCHLOROTHIAZIDE: A NEW RISK: NON-MELANOMA SKIN CANCER (BASAL CELL CARCINOMA, SQUAMOUS CELL CARCINOMA)

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the below listed companies would like to inform you of a new risk of non-melanoma skin cancer (NMSC) (basal cell carcinoma, squamous cell carcinoma) in patients treated with hydrochlorothiazide.

Summary

- Pharmaco-epidemiological 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 to 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 Ultra Violet (UV) rays and to 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 nephrologic oedema or chronic heart insufficiency.

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 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.

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).

Incidence rates of NMSC 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 may increase approx. 4 to 7.7-fold for SCC and 1.3-fold for BCC depending on the cumulative dose of HCTZ.

The affected product labels will be updated to inform on the risk of NMSC associated with the use of HCTZ.

For further information, please contact the respective companies indicated in the table below:

Company	Product	Active Ingredient	Registration Number	Contact Details
Austell Laboratories (Pty) Ltd 1 Sherborne Road, Parktown, Johannesburg, 2193	Lisozide 10	Lisinopril Dihydrate equivalent to Lisinopril 10,0 mg and Hydrochlorothiazide 12,5 mg	A39/7.1.3/0108	Shehnaz Mahomed Tel: 0860 287 8355, 011 611 1603 email: SMahomed@austell.co.za Responsible Pharmacist/ Head of Regulatory Affairs
	Lisozide 20	Lisinopril Dihydrate equivalent to Lisinopril 20,0 mg and Hydrochlorothiazide 12,5 mg	A39/7.1.3/0109	
	Austell Losartan CO 50mg/12.5 mg	Losartan Potassium equivalent to Losartan 50,0 mg and Hydrochlorothiazide 12,5 mg	42/7.1.3/0027	

Alliance Pharma (Pty) Ltd 4 Brewery Street, Isando	Gentiazide tablets	Hydrochlorothiazide 25 mg	U0221	Zibuyile Hadebe Tel: 011 075 8860 Fax: 086 676 5122 email: zibuyile.hadebe@ascendishealth.com Compliance (RA/QA) Manager & PV Officer
Akacia Healthcare (Pty) Ltd 4 Brewery Street, Isando	Lozaan CO 50 mg	Hydrochlorothiazide 12,5 mg and Losartan Potassium 50,0 mg	42/7.1.3/0579	Boitumelo Mailula Tel: 011 075 8886 email: boitumelo.mailula@ascendishealth.com Head of Compliance (RA/QA) Manager & Responsible Pharmacist
	Lozaan CO 100 mg	Hydrochlorothiazide 25 mg and Losartan Potassium 100 mg	42/7.1.3/0580	
Adcock Ingram Holdings Limited 1 New Road, (c/o New Road & 7th Street), Midrand, South Africa	Adco-Retic	Amiloride Hydrochloride 5 mg and Hydrochlorothiazide 50 mg	V/18.1/260	Thavendree Chetty Tel: 011 635 0134 Fax: 086 553 0128 email: adcock.aereports@adcock.com Head: Compliance & Responsible Pharmacist
	Adco-Zetomax CO 10/12,5	Lisinopril 10 mg and Hydrochlorothiazide 12,5 mg	37/7.1.3/0160	
	Adco-Zetomax CO 20/12,5	Lisinopril 20 mg and Hydrochlorothiazide 12,5 mg	37/7.1.3/0162	
Accord Healthcare(Pty) Ltd Building 2, Tuscany Office Park, 6 Coombe Place, Rivonia, Gauteng, South Africa	Losaar Plus 50/12,5	Losartan Potassium 50,0 mg and Hydrochlorothiazide 12,5mg	42/7.1.3/0325	Reshlan Nagoor Tel: 082 494 2510 email: reshlan.nagoor@accordhealth.co.za Responsible Pharmacist & Executive Director Bashier Surve Tel: 082 786 4747 email: bashier@accordhealth.co.za RA Manager
	Losaar Plus 100/25	Losartan Potassium 100,0 mg and Hydrochlorothiazide 25,0mg	42/7.1.3/0326	

AstraZeneca Pharmaceuticals (Pty) Ltd Building 2, Northdowns Office Park, 17 Georgian Crescent West Bryanston, 2191	Atacand PLUS 16/12,5 mg	Candesartan cilexetil 16 mg and Hydrochlorothiazide 12,5 mg	35/7.1.3/0098	Sanjay Lakha Tel: 011 797 6000, 072 758 7638 email: sanjay.lakha@astrazeneca.com ; PatientSafetySouth Africa@astrazeneca.com Responsible Pharmacist
	Atacand PLUS 32/12,5 mg	Candesartan cilexetil 32 mg and Hydrochlorothiazide 12,5 mg	43/7.1.3/0922	
	Atacand PLUS 32/25 mg	Candesartan cilexetil 32 mg and Hydrochlorothiazide 25 mg	43/7.1.3/0923	
	Zestoretic 10	Hydrochlorothiazide 12,5 mg and Lisinopril dihydrate equivalent to lisinopril anhydrous 10 mg	29/7.1.3/0652	
	Zestoretic 20	Hydrochlorothiazide 12,5 mg and Lisinopril dihydrate equivalent to lisinopril anhydrous 20 mg	27/7.1.3/0366	

Health professionals should report all suspected adverse events associated with all hydrochlorothiazide containing medicines to the applicable company indicated above or to the NADEMC (National Drug Event Monitoring Centre) – Telephone: (021) 447 1618 or Fax: (021) 4486181.

Yours faithfully



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Shehnaz Mahomed
Responsible Pharmacist/
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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) 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.