



IMPORTANT MEDICINE SAFETY INFORMATION

07 November 2018

Dear Healthcare Professional

Re: HYDROCHLOROTHIAZIDE: RISK OF 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 including biopsy and histological examinations of biopsies.
- Patients should be advised to limit exposure to sunlight and 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 needs 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 ($\sim 25\ 000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100\ 000$ 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 approximately 4 to 7.7-fold for SCC and 1.3-fold for BCC depending on the cumulative dose of HCTZ.

The 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
Merck (Pty) Ltd	Ziak 2.5/6.25	Bisoprolol fumarate 2.5 mg / Hydrochlorothiazide 6.25 mg	31/7.1.3/0455	Merle Scher Responsible Pharmacist Merle.scher@merckgroup.com
	Ziak 5/6.25	Bisoprolol fumarate 2.5 mg / Hydrochlorothiazide 6.25 mg	31/7.1.3/0456	Darshni Naicker Medical Director Darshni.naicker@merckgroup.com
	Ziak 10/6.25	Bisoprolol fumarate 2.5 mg / Hydrochlorothiazide 6.25 mg	31/7.1.3/0457	Sudhesh Badari SCC PV Manager Sudhesh.badari@merckgroup.com
	Ziabeta 2.5/6.25	Bisoprolol fumarate 2.5 mg / Hydrochlorothiazide 6.25 mg	37/7.1.3/0564	Drug.safety.southeastafrica@merckgroup.com Tel: + 27 11 372 5000 Fax No.: +27 11 372 5304
	Ziabeta 5/6.25	Bisoprolol fumarate 2.5 mg / Hydrochlorothiazide 6.25 mg	37/7.1.3/0610	
	Ziabeta 10/6.25	Bisoprolol fumarate 2.5 mg / Hydrochlorothiazide 6.25 mg	37/7.1.3/0611	
Ingelheim Pharmaceuticals (Pty) Ltd	Co-Micardis 40/12,5 mg	Telmisartan 40 mg/ Hydrochlorothiazide 12,5 mg	35/7.1.3/0096	Pome Khai Responsible Pharmacist pome.khai@boehringer-ingelheim.com
	Co-Micardis 80/12,5 mg	Telmisartan 80 mg/ Hydrochlorothiazide 12,5 mg	35/7.1.3/0097	Erica Zinman Pharmacovigilance Manager PV_local_South_Africa@boehringer-ingelheim.com
	Co-Micardis 80/12,5 mg	Telmisartan 80 mg/ Hydrochlorothiazide 25 mg	42/7.1.3/0766	Tel+ 27 11 348 2400 Fax No: +27 86 407 1026
	Co-Pritor 40/12,5 mg	Telmisartan 40 mg/ Hydrochlorothiazide 12,5 mg	35/7.1.3/0347	
	CO-Pritor 80/12,5 mg	Telmisartan 80 mg/ Hydrochlorothiazide 12,5 mg	35/7.1.3/0348	
Novartis SA (Pty) Ltd	Co-Diovan 160/12.5 mg	Valsartan 160 /Hydrochlorothiazide 12.5 mg	34/7.1.3/0441	Kumeshnie Padayachee Responsible Pharmacist Kumeshnie.padayachee@novartis.com
	Co-Tareg 160/12.5 mg	Valsartan 160 /Hydrochlorothiazide 12.5 mg	41/7.1.3/0743	Nicola Lister Director: Medical & Chief Scientific Officer (CSO) Nicola.lister@novartis.com
	Co-Diovan 160 Plus	Valsartan 160 /Hydrochlorothiazide 25 mg	37/7.1.3/0225	
	Co-Migroben 160/25 mg	Valsartan 160 /Hydrochlorothiazide 25 mg	43/7.1.3/0085	Lesego Mabiletsa Patient Safety Country Head

	Co-Tareg Plus 160/25 mg	Valsartan 160 /Hydrochlorothiazide 25 mg	41/7.1.3/0744	Lesego.mabiletsa@novartis.com
	Co-Diovan 320/12.5 mg	Valsartan 320 /Hydrochlorothiazide 12.5 mg	41/7.1.3/0147	Drug.safetyssa@novartis.com
	Co-Diovan 320/25 mg	Valsartan 320 /Hydrochlorothiazide 25 mg	41/7.1.3/0148	Tel: 0861 929-929 or (+27) 11 347-6600
	Co-Diovan 80/12.5 mg	Valsartan 80 /Hydrochlorothiazide 12.5 mg	32/7.1.3/0336	
	Co-Migroben 80/12.5 mg	Valsartan 80 /Hydrochlorothiazide 12.5 mg	43/7.1.3/0083	
	Co-Tareg 80/12.5 mg	Valsartan 80 /Hydrochlorothiazide 12.5 mg	35/7.1.3/0276	
	Co-Exforge 10/160/12.5 mg	Amlodipine 10/ Valsartan 160 /Hydrochlorothiazide 12.5 mg	44/7.1.3/0077	
	Co-Exforge 10/160/25 mg	Amlodipine 10/ Valsartan 160 /Hydrochlorothiazide 25 mg	44/7.1.3/0078	
	Co-Exforge 10/320/25 mg	Amlodipine 10/ Valsartan 320 /Hydrochlorothiazide 25 mg	44/7.1.3/0079	
	Co-Exforge 5/160/12.5 mg	Amlodipine 5/ Valsartan 160 /Hydrochlorothiazide 12.5 mg	44/7.1.3/0075	
	Co-Exforge 5/160/25 mg	Amlodipine 5/ Valsartan 160 /Hydrochlorothiazide 25 mg	44/7.1.3/0076	
Pfizer Laboratories (Pty) Ltd	Accumax Co 10/12,5	Quinapril 10 mg/ Hydrochlorothiazide 12,5 mg	34/7.1.3/0233	Pharmacovigilance reporting: 24-hour telephone number: 0860 PFIZER (0860 734937)
	Accumax Co 20/12,5	Quinapril 20 mg/ Hydrochlorothiazide 12,5 mg	34/7.1.3/0234	Fax no: Toll-free (local): 080099-9931, Alt. 1: +27 11 895 1600. Alt. 2: +1 973 660 8961
	Accuretic 10/12,5	Quinapril 10 mg/ Hydrochlorothiazide 12,5 mg	27/7.1.3/0165	Email: ZAF.AEReporting@pfizer.com
	Accuretic 20/12,5	Quinapril 20 mg/ Hydrochlorothiazide 12,5 mg	27/7.1.3/0166	Company contact point: Larne Pearson (Responsible Pharmacist/ Team Leader Quality) Tel: +27 11 320 6239 Email: larne.pearson@pfizer.com
Aspen Pharmacare	Amiloretic	HCTZ 50 mg; Amiloride 5 mg	L/18.1/396	Tel: 0800 118 088
	Amiloretic HS	HCTZ 25 mg; Amiloride 2,5 mg	U/18.1/40	Fax: 011 239 6306
	Pharmapress Co Tablet	HCTZ 12, mg; Enalapril maleate 20 mg	34/7.1.3/0190	Email: drugsafety@aspenpharma.com
	Ridaq-12,5	HCTZ 12,5 mg	A39/18.1/0399	
	Ridaq-25	HCTZ 25 mg	M/18.1/35	
	Ridaq-50	HCTZ 50 mg	M/18.1/36	
	Sartoc Co	HCTZ 25 mg; Losartan	42/7.1.3/0288	

	100/25 mg	potassium 100 mg	
	Sartoc-Co 50/12,5	HCTZ 12,5 mg; Losartan potassium 50 mg	41/7.1.3/0956
	Servatrin	HCTZ 25 mg; Timolol maleate 10 mg; Amiloride 2,5 mg	V/7.1.3/354

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



Merck (Pty) Ltd
M. Scher
Responsible Pharmacist



Merck (Pty) Ltd
S. Badari
SCC PV Manager



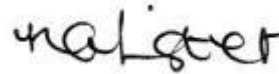
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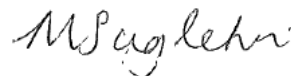
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Aspen Pharmacare Holdings Limited
Lorraine Hill
Group Operating Officer and Responsible Pharmacist



Aspen Pharmacare Holdings Limited
Michelle Singleton
Executive: Group Safety & Pharmacovigilance

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.