



IMPORTANT MEDICINE SAFETY INFORMATION

09 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.
- 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 (~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 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
LITHA PHARMA (PTY) LTD	RENEZIDE	Triamterene 50 mg/ Hydrochlorothiazide 25 mg	U/18.1/72	Drug Safety: Claudette Bartlett Tel: 011 516 1700 Mobile: 0825756121 Email: claudette.bartlett@acino.swiss
MSD (PTY) LTD	CO-RENITEC 20/12,5	Enalapril maleate 20 mg/ Hydrochlorothiazide 12,5 mg	V/7.1.3/119	Pharmacovigilance: Nicky Holl Tel: 011 655 3042 Fax: +27 11 655 3127 Email: pharmacovigilance.zaf@merck.com
	COZAAR COMP	Losartan potassium 50 mg/ Hydrochlorothiazide 12,5 mg	30/7.1.3/0284	
	FORTZAAR	Losartan potassium 100 mg/ Hydrochlorothiazide 25 mg	34/7.1.3/0281	
	MODURETIC 5/50	Amiloride hydrochloride 5 mg/ Hydrochlorothiazide 50 mg	C/18.1/215	
	COZAAR COMP 100/12,5	Losartan potassium 100 mg/ Hydrochlorothiazide 12,5 mg	46/7.1.3/0865	

Company	Product	Active Ingredient	Registration Number	Contact Details
MYLAN (PTY) LTD	MYLACAND PLUS 16/12,5 mg (Tablets)	Candesartan cilexetil 16 mg/ Hydrochlorothiazide 12,5 mg	45/7.1.3/0394	Pharmacovigilance: Mogin Nadasan Tel: +27 71 281 2503 Email: Medinfosa@mylan.com Mylan Customer Care Centre Tel: +27 76 6898484 or +27 11 4511325 Email: mylansa@mylan.com
PHARMA DYNAMICS (PTY) LTD	Bilacor Co 2,5/6,25	Bisoprolol fumarate 2,5 mg/ Hydrochlorothiazide 6,25 mg	44/7.1.3/1010	Tel: 021 707 7000; Fax: 021 702 0533 Email: pharmacovigilance@pharmadynamics.co.za and p.vanvuuren@pharmadynamics.co.za
	Bilacor Co 5/6,25	Bisoprolol fumarate 5 mg/ Hydrochlorothiazide 6,25 mg	44/7.1.3/1011	
	Bilacor Co 10/6,25	Bisoprolol fumarate 10 mg/ Hydrochlorothiazide 6,25 mg	44/7.1.3/1012	
	Enap-Co	Enalapril maleate 20 mg/ Hydrochlorothiazide 12,5 mg	34/7.1.3/0088	
	Lisoretic 10/12,5	Lisinopril 10 mg/ Hydrochlorothiazide 12,5 mg	37/7.1.3/0475	
	Lisoretic 20/12,5	Lisinopril 20 mg/ Hydrochlorothiazide 12,5 mg	37/7.1.3/0476	
	Zartan Co 50/12,5	Losartan potassium 50 mg/ Hydrochlorothiazide 12,5 mg	42/7.1.3/1068	
	Zartan Co 100/25	Losartan potassium 100 mg/ Hydrochlorothiazide 25 mg	42/7.1.3/1069	

Company	Product	Active Ingredient	Registration Number	Contact Details
SANDOZ SA(PTY) LTD	Candepres Plus 16/12,5	Candesartan cilexetil/ hydrochlorothiazide	44/7.1.3/0555	Email: patientsafety.sacg@novartis.com Tel: +27 11 347 6600 Fax: +27 11 929 2262
	Hexazide 25	Hydrochlorothiazide	32/18.1/0419	
	Hexal-Lisinopril Co 20	Lisinopril/ hydrochlorothiazide	37/7.1.3/0632	
	Hexal-Lisinopril Co 10		37/7.1.3/0631	
	Los-arb Comp 50/12,5 mg	Losartan Potassium/ hydrochlorothiazide	43/7.1.3/0867	
	Los-arb Comp 100/25 mg		43/7.1.3/0868	
	Telmisartan Plus Sandoz 40/12.5 mg	Telmisartan/ Hydrochlorothiazide	46/7.1.3/0927	
	Telmisartan Plus Sandoz 80/12.5 mg		46/7.1.3/0928	
	Telmisartan Plus Sandoz 80/25 mg		46/7.1.3/0929	
	Telpres Plus 40/12,5 mg		46/7.1.3/0930.9 27	
	Telpres Plus 80/12,5 mg		46/7.1.3/0931.9 28	
	Telpres Plus 80/25 mg		46/7.1.3/0932.9 29	
	Co-Zomevek 80/12,5 Tablet	Valsartan/ Hydrochlorothiazide	43/7.1.3/0080	
	Co-Zomevek 160/12,5 Tablet		43/7.1.3/0081	
	Co-Zomevek 160/25 Tablet		43/7.1.3/0082	

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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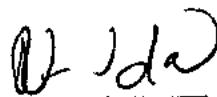
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References

- 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) Pollegard A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Fris S. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; 282: 322- 331.