



IMPORTANT MEDICINE SAFETY INFORMATION

7 June 2019

Dear Healthcare Professional

Re: CONCOMITANT FLUOROQUINOLONES AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs) / ANGIOTENSIN RECEPTOR BLOCKERS USE:

ACUTE KIDNEY INJURY (AKI), ESPECIALLY IN INDIVIDUALS WITH MODERATE TO SEVERE RENAL IMPAIRMENT AND IN ELDERLY PATIENTS

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the below listed companies would like to inform you of a risk of acute kidney injury (AKI) in patients treated concomitantly with ACE inhibitors / Angiotensin Receptor Blockers (ARBs) and fluoroquinolones.

In collaboration with SAHPRA, the Professional Information (PI) and Patient Information Leaflet (PIL) of fluoroquinolones, ACEIs and ARBs will be amended to reflect the above safety information.

Summary

- The concomitant use of fluoroquinolones with ACE inhibitors / Angiotensin Receptor Blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance \leq 30 ml/min) and in elderly patients.
- Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors / Angiotensin Receptor Blockers whether used separately and/or concomitantly.
- Patients currently treated with concomitant use of ACE inhibitors / Angiotensin Receptor Blockers and fluoroquinolones should contact their doctor to re-evaluate their treatment.

Background on the Safety Concern

- A signal detection screening focusing on drug-drug interactions identified 16 reports, showing disproportionate reporting of a combination of ciprofloxacin, enalapril and AKI in VigiBase®, the WHO global database of individual case safety reports (ICSR)¹.
- Among the 16 reports, 5 had an alternative explanation for AKI than a nephrotoxic effect of ciprofloxacin alone or an interaction with enalapril. Analysis of the 11 remaining cases indicated that in most patients, the event did not occur until after recent ciprofloxacin prescription, lending weight to ciprofloxacin or a combined action of ciprofloxacin and enalapril being the cause.
- The literature analysis presented in the publication Signal April 2017² from the Uppsala Monitoring Centre, a nested case-control study in older men³, describes a greater than additive risk of developing acute kidney injury with the concomitant use of fluoroquinolones and renin-angiotensin receptor blockers.
- The interaction between ACEIs/ARBs and fluoroquinolones leading to AKI appears to be a class effect.

References:

1. Savage R: Ciprofloxacin, enalapril and acute kidney injury: Strengthening of a drug Interaction signal. WHO Pharmaceuticals Newsletter : 16-21, No. 1, 2018 Available from: URL : http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No1-2018.pdf?ua=1
2. Savage R: Ciprofloxacin, Enalapril and Acute Kidney Injury: Strengthening of a Drug Interaction Signal. SIGNAL 2017, Uppsala Monitoring Centre and New Zealand.
3. Bird ST, Etmnan M, Brophy JM, Hartzema AG, Delaney JAC: Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ 2013; 185: E475-E482

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

Company	Product	Active ingredient	Registration Number	Contact details
Activo Health (Pty) Ltd	Acti-Prex	Perindopril Tert-Butylamine 4 mg	41/7.1.3/0175	Tel: 012 848 7600/ 0800 22 84 86 Email: info@activo.co.za
Austell Laboratories (Pty) Ltd	Austell Enalapril 5 mg	Enalapril	A48/7.1.3/0922	Shehnaz Mahomed Tel: 011 611 1603 Cell: 082 619 7869 Email: smahomed@austell.co.za
	Austell Enalapril 10 mg	Enalapril	A48/7.1.3/0923	
	Austell Enalapril 20 mg	Enalapril	A48/7.1.3/0924	
	Austell Lisinopril 10 mg	Lisinopril	27/7.1.3/0032	
	Austell Lisinopril 20 mg	Lisinopril	27/7.1.3/0392	
	Austell Losartan 50 mg	Losartan	41/7.1.3/0497	
	Austell Losartan 100 mg	Losartan	41/7.1.3/0498	
	Austell Losartan Co 50/ 12,5 mg	Losartan/ HCTZ	42/7.1.3/0027	
	Austell Ramipril 2,5 mg	Ramipril	A39/7.1.3/0240	
	Austell Ramipril 5 mg	Ramipril	A39/7.1.3/0241	
	Austell Ramipril 10 mg	Ramipril	A39/7.1.3/0242	

Company	Product	Active ingredient	Registration Number	Contact details
	Lisozide 10 mg	Lisinopril/ HCTZ	A39/7.1.3/0108	
	Lisozide 20 mg	Lisinopril/ HCTZ	A39/7.1.3/0109	
	Austell Ciprofloxacin 250 mg	Ciprofloxacin hydrochloride 250 mg	38/20.1.1/0011	
	Austell Ciprofloxacin 500 mg	Ciprofloxacin hydrochloride 500 mg	38/20.1.1/0012	
	Austell Levofloxacin 250 mg	Levofloxacin hemihydrate 250 mg	41/20.1.1/1018	
	Austell Levofloxacin 500 mg	Levofloxacin hemihydrate 500 mg	41/20.1.1/1019	
	Austell Moxifloxacin IV 400 mg/250 ml	Moxifloxacin hydrochloride	50/20.1.1/0434	
	Floquin IV 2mg/ ml	Ciprofloxacin	50/20.1.1/1035	
Camox Pharmaceuticals (Pty) Ltd	Austell Ofloxacin 200 mg	Ofloxacin 200 mg	A39/20.1.1/0149	Irefaan Mahomed Tel: 011 611 1605 Cell: 083 633 8781 Email: irefaanm@austell.co.za
	Austell Ofloxacin 400 mg	Ofloxacin 400 mg	A39/20.1.1/0150	
Dezzo Trading 392 (Pty) Ltd	Ciprofloxacin Unicorn 250	Each 250 mg tablet Contains Ciprofloxacin Hydrochloride Equivalent to Ciprofloxacin	44/20.1.1/0538	Tel: 011 075 8918 Fax: 086 677 2110 e-mail: drugsafety@ascendishealth.com
	Ciprofloxacin Unicorn 500	Each 500 mg tablet Contains Ciprofloxacin Hydrochloride Equivalent to Ciprofloxacin	44/20.1.1/0539	
	Ciprofloxacin Unicorn 750	Each 750 mg tablet Contains Ciprofloxacin Hydrochloride Equivalent to Ciprofloxacin	44/20.1.1/0540	
	Ciprocina	Each 1,0 ml Solution Contains ciprofloxacin lactate Equivalent to ciprofloxacin 2 mg	A40/20.1.1/0114	

Company	Product	Active ingredient	Registration Number	Contact details
	Profloxin 250	Each 250 mg tablet Contains Ciprofloxacin Hydrochloride Equivalent to Ciprofloxacin	44/20.1.1/0541	
	Profloxin 500	Each 500 mg tablet Contains Ciprofloxacin Hydrochloride Equivalent to Ciprofloxacin	44/20.1.1/0542	
	Profloxin 750	Each 750 mg tablet Contains Ciprofloxacin Hydrochloride Equivalent to Ciprofloxacin	44/20.1.1/0543	
	Enalapril Ascendis 5 mg	Enalapril maleate 5 mg	35/7.1.3/0283	
	Enalapril Ascendis 10 mg	Enalapril maleate 10 mg	35/7.1.3/0284	
Hetero Drugs SA Pty Ltd	Floxave 400	Moxifloxacin 400 mg	48/20.1.1/0021	For reporting ADRs Tel: 012 644 2120/ 0827874995 Fax: 012 644 1564 email addresses – Nokuthula.n@heterodrugs.com pvg.cdma@heterodrugs.com
Litha Pharma (Pty) Ltd	Litha Levofloxacin 250 mg tablets	Levofloxacin Hemihydrate	42/20.1.1/0509	Tel: +27 60 998 7896 Email: drugsafety_ZA@acino.swiss Nerine.duplessis@acino.swiss
	Litha Levofloxacin 500 mg tablets	Levofloxacin Hemihydrate	42/20.1.1/0510	
	Orpic 250 mg tablets	Ciprofloxacin Hydrochloride	35/20.1.1/0101	
	Orpic 500 mg tablets	Ciprofloxacin Hydrochloride	35/20.1.1/0102	
	Orpic 2 mg/ ml IV	Ciprofloxacin Lactate	A40/20.1.1/0454	
Macleods Pharmaceuticals SA	Lonxave 400	Moxifloxacin 400 mg	48/20.1.1/0024	Tel: 011 682 1169 Cell: 083 285 0621 Cell: 082 450 6204 Fax: 086 698 2015 shahaboodeenc@macleodspharma.com ; rgosai@macleodspharma.com
	Avrokel 250 mg (previously Macleods Levofloxacin 250 mg)	Levofloxacin 250 mg	45/20.1.1/0684	


Company	Product	Active ingredient	Registration Number	Contact details
	Avrokel 500 mg (previously Macleods Levofloxacin 500 mg)	Levofloxacin 500 mg	45/20.1.1/0685	
	Losartan Macleods 50 mg	Losartan Potassium 50 mg	46/7.1.3/0205	
	Losartan Macleods 100 mg	Losartan Potassium 100 mg	46/7.1.3/0206	
Mylan (Pty) Ltd	Ciprogen IV 200 mg/100 ml (Solution).	Ciprofloxacin 2 mg/ml	A40/20.1.1/0618	Pharmacovigilance: Tel: +27 71 281 2503 Email: medinfos@mylan.com Mylan Customer Care Centre: Tel: +27 76 689 8484
	Mizart 40 mg,	Telmisartan 40 mg;	45/7.1.3/0606,	
	Mizart 80 mg (Tablets).	Telmisartan 80 mg	45/7.1.3/0607	
	Mylacand 8 mg,	Candesartan cilexetil 8 mg;	45/7.1.3/0301,	
	Mylacand 16 mg (Tablets).	Candesartan cilexetil 16 mg	45/7.1.3/0302	
	Mylacand Plus 16/12,5 mg (Tablets).	Candesartan cilexetil 16 mg/ Hydrochlorothiazide 12,5 mg	45/7.1.3/0394.	
	Mylan Captopril 25,	Captopril 25 mg;	29/7.1/0228,	
	Mylan Captopril 50 (Tablets).	Captopril 50 mg	32/7.1/0528	
Xixia Pharmaceuticals (Pty) Ltd (a Mylan Company)	Mylan Levofloxacin 250 mg,	256,23 mg levofloxacin hemihydrate equivalent to 250 mg levofloxacin;	43/20.1.1/0841,	Pharmacovigilance: Tel: +27 71 281 2503 Email: medinfos@mylan.com Mylan Customer Care Centre: Tel: +27 76 689 8484
	Mylan Levofloxacin 500 mg (Film-coated tablets).	512,46 mg levofloxacin hemihydrate equivalent to 500 mg levofloxacin	43/20.1.1/0842	
	Ciprogen 250 mg,	Ciprofloxacin hydrochloride monohydrate equivalent to 250 mg ciprofloxacin;	36/20.1.1/0428,	
	Ciprogen 500 mg (Film-coated tablets).	Ciprofloxacin hydrochloride monohydrate equivalent to 500 mg ciprofloxacin	36/20.1.1/0429	


Company	Product	Active ingredient	Registration Number	Contact details
Pharmaceutical Contractors (Pty) Ltd	Hypace 5 mg Tablets	Enalapril Maleate 5,0 mg	33/7.1.3/0452	Tel: 011 974 1631 Email: claudem@pharmacon.co.za
Pharmaplan (Pty) Ltd	Zaneril 10/10 tablets	Enalapril Maleate 10 mg; Lercanidipine Hydrochloride 10 mg	41/7.1/0935;	Tel: +27 60 998 7896 Email: freda@loggerenberg@acino.swiss drugsafety_ZA@acino.swiss
	Zaneril 10/20 tablets	Enalapril Maleate 10 mg; Lercanidipine Hydrochloride 20 mg	41/7.1/0936	
Specpharm (Pty) Ltd	Spec Topistin	Ciprofloxacin 200 mg/ml	37/20.1.1/0655	Tel: 011 652 0400 Fax: 011 652 0448 e-mail: pv@specpharm.co.za
	Spec Perindopril Plus 2	Perindopril 2 mg; Indapamide 0,625 mg	41/7.1.3/0630	
	Spec Perindopril Plus 4	Perindopril 4 mg; Indapamide 1,25 mg	41/7.1.3/0631	
	Spec Perindopril 4	Perindopril 4 mg	41/7.1.3/0652	
	Spec Perindopril 8	Perindopril 8 mg	41/7.1.3/0653	
	Netrasol Co 50	Losartan potassium 50 mg; Hydrochlorothiazide 12,5 mg	41/7.1.3/1000	
	Netrasol Co 100	Losartan potassium 100 mg; Hydrochlorothiazide 25 mg	41/7.1.3/1001	
	Spec Losartan 100	Losartan 100 mg	41/7.1.3/1075	
	Spec Losartan 50	Losartan 50 mg	41/7.1.3/1076	
Trinity Pharma	Normoten 50	Losartan potassium	42/7.1.3/0437	Tel: 010 594 5610 Email: tsiane.makou@trinitypharma.co.za
	Normoten 100	Losartan potassium	42/7.1.3/0438	
	Co-Normoten 50/12,5 mg	Losartan potassium and hydrochlorothiazide	42/7.1.3/0857	
	Co-Normoten 100/25 mg	Losartan potassium and hydrochlorothiazide	42/7.1.3/0858	

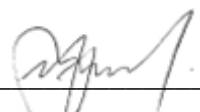
Company	Product	Active ingredient	Registration Number	Contact details
Unicorn Pharmaceuticals (Pty) Ltd	Lisinopril Co Unicorn 10/12,5	Lisinopril 10,0 mg and Hydrochlorothiazide 12,5 mg	37/7.1.3/0477	Tel: 021 460 1952 Fax: 021 467 3952 e-mail: enquiries@unicornpharma.co.za
	Lisinopril Co Unicorn 20/12,5	Lisinopril 20,0 mg and Hydrochlorothiazide 12,5 mg	37/7.1.3/0478	
	Vasovan 80	Valsartan 80 mg	46/7.1.3/0951	
	Vasovan 160	Valsartan 160 mg	46/7.1.3/0952	


Healthcare Professionals should report all suspected adverse events associated with all ACE inhibitors and fluoroquinolones to the applicable company indicated above, or to the SAHPRA Pretoria Office at Tel: 012 842 7609/10, Email: adr@sahpra.org.za or the National Adverse Drug Event Monitoring Centre at Tel: 021 447 1618 or Fax 021 448 6181.

Yours faithfully,


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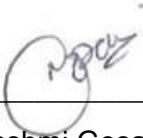

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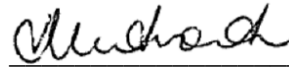
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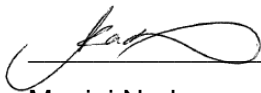
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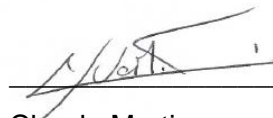
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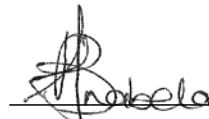
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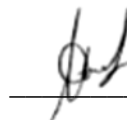
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