



IMPORTANT MEDICINE SAFETY INFORMATION

26 June 2019

Dear Healthcare Professional

Re: CONCOMITANT FLUOROQUINOLONES AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs) OR 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 ACEIs / 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 2017 ² from the Uppsala Monitoring Centre; a nested case-control study in older men ³, 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 Name	Active Ingredient(s)	Registration Number	Contact Details
Actavis Pharma (Pty) Ltd a subsidiary of Teva Pharmaceutical Industries (marketed by Astral Health Care (Pty) Ltd) 1 st Floor, Building 3, Maxwell Office Park, Magwa Crescent West. Waterfall City, Midrand, 2090	Artav 250 (film coated tablet)	Levofloxacin	43/20.1.1/0370	Tel: 011 055 0200 Fax: 011 388 2688 Email: Safety.South-Africa@teva.co.il
	Artav 500 (film coated tablet)	Levofloxacin	43/20.1.1/0371	
	Artav 750 (film coated tablet)	Levofloxacin	43/20.1.1/0372	
	Ciprol 250	Ciprofloxacin	37/20.1.1/0573	
	Ciprol 500	Ciprofloxacin	37/20.1.1/0574	
Adcock Ingram (Pty) Limited 1 New Road Midrand 1685 South Africa	Adco Ciprofloxacin 2 mg/ml	Ciprofloxacin	39/20.1.1/0646	Tel: 011 635 0134 Fax: 086 553 0128 Email: adcock.aereports@adcock.com
	Adco Zetomax 5 mg	Lisinopril	33/7.1.3/0513	
	Adco Zetomax 10 mg	Lisinopril	33/7.1.3/0514	
	Adco Zetomax 20 mg	Lisinopril	33/7.1.3/0515	
	Adco Zetomax Co 10/12,5	Lisinopril and hydrochlorothiazide	37/7.1.3/0160	
	Adco Zetomax Co 20/12,5	Lisinopril and hydrochlorothiazide	37/7.1.3/0162	
Akacia Healthcare (Pty) Ltd 4 Brewery Street, Isando	ACAQUIN 250 (film coated tablets)	Levofloxacin	42/20.1.1/0859	Tel: 011 075 8860 Fax: 086 676 5122 Email: zibuyile.hadebe@ascendishealth.com / boitumelo.mailula@ascendishealth.com
	ACAQUIN 500 (film coated tablets)	Levofloxacin	42/20.1.1/0860	
	Envas 2.5	Enalapril maleate	34/7.1.3/0334	
	Envas 5	Enalapril maleate	34/7.1.3/0335	
	Envas 10	Enalapril maleate	34/7.1.3/0336	
AstraZeneca Pharmaceuticals (Pty) Limited 17 Georgian Crescent, Northdowns Office Park, Building 2, Bryanston, 2191	Atacand 8 mg	Candesartan cilexetil	32/7.1.3/0099	Andiswa Lawana Tel: 011 797 6000, 072 758 7638 Email: patientsafetysouthafrica@astrazeneca.com
	Atacand 16 mg	Candesartan cilexetil	32/7.1.3/0100	
	Atacand 32 mg	Candesartan cilexetil	39/7.1.3/0244	
	Atacand Plus 16/12,5 mg	Candesartan cilexetil and 12,5 mg hydrochlorothiazide	35/7.1.3/0098	
	Atacand Plus 32/12,5mg	Candesartan cilexetil and hydrochlorothiazide	43/7.1.3/0922	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Atacand Plus 32/25 mg	Candesartan cilexetil and hydrochlorothiazide	43/7.1.3/0923	
	Zestril 5	Lisinopril	V/7.1.3/160	
	Zestril 10	Lisinopril	V/7.1.3/161	
	Zestril 20	Lisinopril	V/7.1.3/162	
	Zestoretic 10	Lisinopril and hydrochlorothiazide	29/7.1.3/0652	
Aurobindo Pharma (Pty) Ltd Woodhill Office Park, Building 1 53 Phillip Engelbrecht Avenue Meyersdal, Ext 12, 1448 Johannesburg	Loxip 500 mg	Ciprofloxacin	41/20.1.1/1053	Tel: 011 867 9100 Fax: 011 867 9111 Email: pv.za@aurobindo.com
	Annin 50 mg	Losartan	43/7.1.3/0494	
	Annin 100 mg	Losartan	43/7.1.3/0495	
	Reprex 4 mg	Perindopril tert-butylamine	43/7.1.3/1033	
	Reprex 8 mg	Perindopril tert-butylamine	43/7.1.3/1034	
	Kwinco10/ 12,5 mg	Quinapril + hydrochlorothiazide	43/7.1.3/1046	
Cipla Medpro (Pty) Ltd and Cipla Life Sciences (Pty) Ltd Building 9, Parc du Cap Office Park Mispel Road Bellville 7530	Mofloxx	Moxifloxacin	44/20.1.1/1063	Tel: 021 943 4200 Fax: 021 914 1587 Email: drugsafetysa@Cipla.com
	Octin	Ofloxacin	36/15.1/0002	
	Ciploxx 250	Ciprofloxacin	36/20.1.1/0376	
	Ciploxx 500	Ciprofloxacin	36/20.1.1/0377	
	Ciprofloxacin Actor 250	Ciprofloxacin	37/20.1.1/0079	
	Ciprofloxacin Actor 500	Ciprofloxacin	37/20.1.1/0080	
	Tavalox 250	Levofloxacin	41/20.1.1/0007	
	Tavalox 500	Levofloxacin	41/20.1.1/0008	
	Tavalox 750	Levofloxacin	41/20.1.1/0009	
	Utin 400	Norfloxacin	34/20.1.1/0059	
	Norfloxacin Actor 400	Norfloxacin	31/20.1.1/0517	
	Cipla Perindopril 2	Perindopril	41/7.1.3/0673	
	Cipla Perindopril 4	Perindopril	41/7.1.3/0674	
	Cipla Perindopril 8	Perindopril	41/7.1.3/0675	
Dr Reddy's Laboratories (Pty) Ltd 1 Sandton Drive Sandton	Cifloc 250	Ciprofloxacin	34/20.1.1/0308	Tel: 011 324 2100 AdverseEvents.SA@drreddys.com
	Cifloc 500	Ciprofloxacin	34/20.1.1/0309	
	DRL Moxifloxacin 400	Moxifloxacin	42/20.1.1/0442	
Fresenius Kabi South Africa	Ciprofloxacin Fresenius 2 mg/ml 100 ml	Ciprofloxacin hydrogen sulphate	45/20.1.1/0798	Tel: 011 545 0154 Email: safety.fksa@fresenius-kabi.com
	Ciprofloxacin Fresenius 2 mg/ml 200 ml	Ciprofloxacin hydrogen sulphate	45/20.1.1/0799	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Levofloxacin 100ml	Levofloxacin hemihydrate	45/20.1.1/0139	
Novagen Pharma Office 2, 100 Sovereign Drive, Route 21 Corporate Park, Nellmapius Drive, Irene, Pretoria, South Africa	Bindace 4 mg	Perindopril	43/7.1.3/1040	Tel: 012 345 3175 Cell: 072 281 3461 / 076 4224 334 Email: telanie@novagenpharma.co.za / elizma@novagenpharma.co.za
	Bindace 8 mg	Perindopril	43/7.1.3/1041	
	Flopro 500 mg	Ciprofloxacin HCl	45/20.1.1/0199	
	Lizro 5 mg	Lisinopril	A40/7.1.3/0722	
	Lizro 10 mg	Lisinopril	A40/7.1.3/0723	
	Lizro 20 mg	Lisinopril	A40/7.1.3/0724	
	Rasol 50 mg	Losartan	43/7.1.3/0497	
	Rasol 100 mg	Losartan	43/7.1.3/0497	
MSD (Pty) Ltd 117 – 16 th Road Private Bag 3 Halfway House 1685 South Africa	Amzaar 5/50	Amlodipine Losartan Potassium	46/7.1.3/0559	Pharmacovigilance: Nicky Holl Tel: 011 655 3042 Fax: 011 655 3127 e-mail: pharmacovigilance.za@merck.com
	Amzaar 5/100	Amlodipine Losartan Potassium	46/7.1.3/0560	
	Co-Renitec 20/12,5	Enalapril maleate Hydrochlorothiazide	V/7.1.3/119	
	Cozaar 50	Losartan Potassium	29/7.1.3/0268	
	Cozaar 100	Losartan Potassium	36/7.1.3/0490	
	Cozaar Comp 50/12,5	Losartan Potassium Hydrochlorothiazide	30/7.1.3/0284	
	Cozaar Comp 100/12,5	Losartan Potassium Hydrochlorothiazide	46/7.1.3/0865	
	Fortzaar	Losartan Potassium Hydrochlorothiazide	34/7.1.3/0281	
Pharma Dynamics 1 st Floor, Grapevine House Steenberg Office Park Silverwood Close West Lake Cape Town 7945	Dynafloc 500	Ciprofloxacin Hydrochloride	34/20.1.1/0405	Tel: 021 707 7000; Fax: 021 702 0533 Email: pharmacovigilance@pharmadynamics.co.za and p.vanvuuren@pharmadynamics.co.za
	Dynarb 150 mg	Irbesartan	43/7.1.3/0720	
	Dynarb 300 mg	Irbesartan	43/7.1.3/0721	
	Enap 5 mg	Enalapril maleate	34/7.1.3/0085	
	Enap 10 mg	Enalapril maleate	34/7.1.3/0086	
	Enap 20 mg	Enalapril maleate	34/7.1.3/0087	
	Enap Co	Enalapril maleate and hydrochlorothiazide	34/7.1.3/0088	
	Levonic IV	Levofloxacin	42/20.1.1/0998	
Lisoretic 10/12,5	Lisinopril dihydrate and hydrochlorothiazide	37/7.1.3/0475		

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Lisoretic 20/12,5	Lisinopril dihydrate and hydrochlorothiazide	37/7.1.3/0476	
	Pearinda 4	Perindopril tert-butylamine	41/7.1.3/0649	
	Pearinda 8	Perindopril tert-butylamine	41/7.1.3/0650	
	Pearinda Plus 4	Perindopril tert-butylamine /Indapamide	41/7.1.3/0633	
	Tesar 40 mg	Telmisartan	45/7.1.3/0978	
	Tesar 80 mg	Telmisartan	45/7.1.3/0979	
	Zartan 50 mg	Losartan potassium	41/7.1.3/0287	
	Zartan 100 mg	Losartan potassium	41/7.1.3/0289	
	Zartan Co 50/12.5	Losartan and hydrochlorothiazide	42/7.1.3/1068	
	Zartan Co 100/25	Losartan and hydrochlorothiazide	42/7.1.3/1069	

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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