



IMPORTANT MEDICINE SAFETY INFORMATION

19 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
Aspen Pharmacare	Tafloc 400 mg	Ofloxacin	35/20.1.1/0175	Tel: 0800 118 088, Fax: 011 239 6306, E-mail: drugsafety@aspenpharma.com
	Tafloc 200 mg	Ofloxacin	35/20.1.1/0174	
	Litares	Moxifloxacin	42/20.1.1/0142	
	Factive 320 mg	Gemifloxacin	35/20.1.1/0058	
	Pharmapress Co Tablet	Hydrochlorothiazide; Enalapril maleate	34/7.1.3/0190	
	Pharmapress 20 mg	Enalapril maleate	33/7.1.3/0480	
	Pharmapress 10 mg	Enalapril maleate	33/7.1.3/0479	
	Pharmapress 5 mg	Enalapril maleate	A38/7.1.3/0640	
	Rampil 10 mg	Ramipril	A39/7.1.3/0144	
	Rampil 5 mg	Ramipril	A39/7.1.3/0143	
	Rampil 2.5 mg	Ramipril	A39/7.1.3/0142	
	Rampil 1.25 mg	Ramipril	A39/7.1.3/0141	
	Sartoc Co 100/25mg	Hydrochlorothiazide; Losartan potassium	42/7.1.3/0288	
	Sartoc-Co 50/12,5	Hydrochlorothiazide; Losartan potassium	41/7.1.3/0956	
Ranbaxy (SA)(Pty) Ltd	Tavanic 500 (Tablets)	Levofloxacin	32/20.1.1/0124	Tel: 012 643 2033/011 495 0117 Fax: 0126432001/3 Email: Susan.heritage@sunpharma.com Barryjames.lewis@sunpharma.com
	Tavanic I.V. 500	Levofloxacin	32/20.1.1/0125	
	Tavanic I.V. 750	Levofloxacin	43/20.1.1/0948	
	Telgen 40	Telmisartan	45/7.1.3/0610	
	Telgen 80	Telmisartan	45/7.1.3/0611	
Ranbaxy Pharmaceuticals (Pty) Ltd	Floxin	Norfloxacin 400 mg	32/20.1.1/0377	Tel: 011 495 0181/011 495 0117 Fax: 011 495 0150 Email: Geeta.ghela@sunpharma.com Barryjames.lewis@sunpharma.com
	Cifran 250 Tablet	Ciprofloxacin	33/20.1.1/0365	
	Cifran 500 Tablets	Ciprofloxacin	33/20.1.1/0366	
	Avebact 400	Moxifloxacin	41/20.1.1.1/0778	
	Tavanic 250 (Tablets)	Levofloxacin	32/20.1.1/0123	
	Tavanic I.V 250	Levofloxacin	32/20.1.1/0002	
	Tavanic 750 (Tablets)	Levofloxacin	43/20.1.1/0947	
	Alapren 5	Enalapril maleate	34/7.1.3/0014	
	Alapren 10	Enalapril maleate	34/7.1.3/0015	
	Alapren 20	Enalapril maleate	34/7.1.3/0016	
	Enalapril Unicorn 5	Enalapril maleate	34/7.1.3/0010	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Enalapril Unicorn 10	Enalapril maleate	34/7.1.3/0011	
	Enalapril Unicorn 20	Enalapril maleate	34/7.1.3/0012	
	Sinopren 5 Tablets	Lisinopril	34/7.1.3/0209	
	Sinopren 10 Tablets	Lisinopril	34/7.1.3/0210	
	Sinopren 20 Tablets	Lisinopril	34/7.1.3/0211	
	Ran Perindopril 4	Perindopril tert-butylamine	42/7.1.3/0107	
	Losartan Co Unicorn 100/25	Losartan; Hydrochlorothiazide	41/7.1.3/1034	
	Losartan Co Unicorn 50/12,5	Losartan; Hydrochlorothiazide	41/7.1.3/1031	
	Lysin 5	Lisinopril	41/7.1.3/ 0116	
	Lysin 10	Lisinopril	41/ 7.1.3 / 0117	
	Lysin 20	Lisinopril	41 / 7.1.3 / 0118	
	Zydus Healthcare SA (Pty) LTD	Zy bact 250 mg	Levofloxacin 250 mg	
Zy bact 500 mg		Levofloxacin 500 mg	44/20.1.1/0250	
Zyace		Perindopril erbumine 4 mg	44/7.1.3/0504	
Ciplasyl Plus4		Perindopril & Indapamide 4/1.25 mg	44/7.1.3/0503	
Diace Co 20/12,5		Lisinopril; Hydrochlorothiazide	41/7.1.3/0042	
Losacar Co 50/12,5		Losartan; Hydrochlorothiazide	41/7.1.3/0087	
Isart Co 150		Irbesartan; Hydrochlorothiazide 150/12,5	45/7.1.3/0073	
Isart Co 300		Irbesartan; Hydrochlorothiazide 300/12,5	45/7.1.3/0074	
Isart 75		Irbesartan 75 mg	43/7.1.3/0269	
Isart 150		Irbesartan 150 mg	43/7.1.3/0283	
Isart 300		Irbesartan 300 mg	43/7.1.3/0291	
Takeda (Pty) Ltd	Deblaston capsules	Pipemidic acid, 200 mg	S/18.5/42	Tel: 011 514 3000 Fax: 011 514 3007 E-mail: DSO-ZA@takeda.com
Sandoz SA (Pty) Ltd	Candepres Plus	Candesartan cilexetil/ hydrochlorothiazide	44/7.1.3/0555	E-mail address: patientsafety.sacq@novartis.com Tel: +27 11 347 6600 Fax: +27 11 929 2262
	HR Enalapril maleate 5	Enalapril maleate	33/7.1.3/0506	
	HR Enalapril maleate 10	Enalapril maleate	33/7.1.3/0507	
	HR Enalapril maleate 20	Enalapril maleate	33/7.1.3/0508	

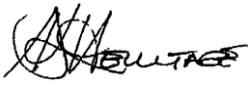
Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Hexal-Lisinopril 5	Lisinopril	35/7.1.3/0225	
	Hexal-Lisinopril 10	Lisinopril	35/7.1.3/0226	
	Hexal-Lisinopril 20	Lisinopril	35/7.1.3/0227	
	Hexal-Lisinopril Co 10	Lisinopril/ hydrochlorothiazide	37/7.1.3/0631	
	Hexal-Lisinopril Co 20	Lisinopril/ hydrochlorothiazide	37/7.1.3/0632	
	Los-Arb 50	Losartan potassium	A40/7.1.3/0063	
	Los-Arb Comp 50/12,5	Losartan potassium/ hydrochlorothiazide	43/7.1.3/0867	
	Los-Arb Comp 100/12,5	Losartan potassium/ hydrochlorothiazide	43/7.1.3/0868	
	Ramipril-HEXAL 2.5	Ramipril	37/7.1.3/0511	
	Ramipril-HEXAL 5	Ramipril	37/7.1.3/0512	
	Ramipril-Hexal 10	Ramipril	A40/7.1.3/0683	
	Telpres Plus 40/12,5 mg	Telmisartan/ Hydrochlorothiazide	46/7.1.3/0930.927	
	Telpres Plus 80/12,5 mg	Telmisartan/ Hydrochlorothiazide	46/7.1.3/0931.928	
	Telpres Plus 80/25 mg	Telmisartan/ Hydrochlorothiazide	46/7.1.3/0932.929	
	Co-Zomevek 80/12.5	Valsartan/ Hydrochlorothiazide	43/7.1.3/0080	
	Co-Zomevek 160/12.5	Valsartan/ Hydrochlorothiazide	43/7.1.3/0081	
	Co-Zomevek 160/25	Valsartan/ Hydrochlorothiazide	43/7.1.3/0082	
	Zomevek 80	Valsartan	43/7.1.3/0036	
	Zomevek 160	Valsartan	43/7.1.3/0037	
	Cipro-Hexal 250	Ciprofloxacin	36/20.1.1/0170	
	Cipro-Hexal 500	Ciprofloxacin	36/20.1.1/0171	
	Cipro-Hexal 750	Ciprofloxacin	36/20.1.1/0172	
	Sandoz Levofloxacin (tablets) 250	Levofloxacin	A40/20.1.1/0525	
	Sandoz Levofloxacin (tablets) 500	Levofloxacin	A40/20.1.1/0526	
Roche Products (Pty) Ltd	Inhibace 5 mg	Cilazapril 5 mg	Y/7.1.3/66	Drug Safety Unit Tel: +27 11 502 5000

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Inhibace Plus	Cilazapril 5 mg and Hydrochlorothiazide 12,5 mg	29/7.1.3/0022	Fax:+27 11 268 5748 email: sa_ssa.drugsafety@roche.com
Abbott Laboratories S.A (Pty) Ltd	Tarka 180/2	180 mg Verapamil hydrochloride/2 mg trandolapril	A39/7.1.3/0508	Shivani Patel Email: Shivani.patel@abbott.com
	Tarka 240/4	240 mg Verapamil hydrochloride/4 mg trandolapril	A39/7.1.3/0547	
	Mavik 2 mg	2 mg trandolapril	28/7.1.3/0263	
Servier Laboratories	Coversyl 4 mg	Perindopril tert-butylamine	X/7.1.3/314	C. Truter Tel: 011 525 3400 celeste.truter@servier.com
	Coversyl Plus	Perindopril tert-butylamine and Indapamide	33/7.1.3/0363	
	Coversyl 10 mg	Perindopril arginine	A39/7.1.3/0236	
	Coveram 5/5; 5/10; 10/55; 10/10	Perindopril arginine and amlodipine	43/7.1.3/0933/4/5/6	
	Preterax	Perindopril tert-butylamine and Indapamide	33/7.1.3/0362	
	Perindopril Co Unicorn 4/1,25	Perindopril tert-butylamine and Indapamide	37/7.1.3/0356	
Biogaran	Bioprexum Plus 10/2,5	Perindopril arginine and indapamide	43/7.1.3/0971	C. Truter Tel: 011 525 3400 celeste.truter@servier.com
	Prexum 4 mg	Perindopril tert-butylamine	36/7.1.3/0020	
	Prexum Plus	Perindopril tert-butylamine and Indapamide	38/7.1.3/0028	
	Prexum 5	Perindopril arginine	A39/7.1.3/0232	
	Prexum 2,5 Plus	Perindopril arginine and indapamide	42/7.1.3/0165	
	Prexum 5 Plus	Perindopril arginine and indapamide	42/7.1.3/00168	
	Prexum 10	Perindopril arginine	A39/7.1.3/0233	
	Vectoryl 4	Perindopril tert-butylamine	34/7.1.3/0480	
	Vectoryl 8	Perindopril tert-butylamine	38/7.1.3/0116	
	Vectoryl Plus	Perindopril tert-butylamine and indapamide	38/7.1.3/0027	
	Perindopril Unicorn 4	Perindopril tert-butylamine	37/7.1.3/0021	
	Perindopril Unicorn 8	Perindopril tert-butylamine	38/7.1.3/0121	
	Circator 4 mg	Perindopril tert-butylamine	36/7.1.3/0021	
	Circator 8 mg	Perindopril tert-butylamine	38/7.1.3/0118	

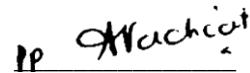
Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Circator Plus	Perindopril tert-butylamine and indapamide	38/7.1.3/0026	
Ingelheim Pharmaceuticals (Pty) Ltd	Micardis 40 mg	Telmisartan	33/7.1.3/0020	Pome Khai Responsible Pharmacist pome.khai@boehringer-ingenheim.com Erica Zinman Pharmacovigilance Manager PV_local_South_Africa@boehringer-ingenheim.com Tel+ 27 11 348 2400 Fax No: +27 86 407 1026
	Pritor 40 mg	Telmisartan	33/7.1.3/0022	
	Micardis 80 mg	Telmisartan	33/7.1.3/0021	
	Pritor 80 mg	Telmisartan	33/7.1.3/0023	
	Co-Micardis 80/12,5 mg	Telmisartan/Hydrochlorothiazide	35/7.1.3/0097	
	Co-Pritor 80/12,5 mg	Telmisartan/Hydrochlorothiazide	35/7.1.3/0348	
	Co-Micardis 40/12,5 mg	Telmisartan/Hydrochlorothiazide	35/7.1.3/0096	
	Co-Pritor 40/12,5 mg	Telmisartan/Hydrochlorothiazide	35/7.1.3/0347	
	Co-Micardis 80/25 mg	Telmisartan/Hydrochlorothiazide	42/7.1.3/0766	
	Twynsta 40/5 mg	Telmisartan/Amlodipine	44/7.1.3/0857	
	Twynsta 40/10 mg	Telmisartan/Amlodipine	44/7.1.3/0858	
	Twynsta 80/5 mg	Telmisartan/Amlodipine	44/7.1.3/0859	
	Twynsta 80/10 mg	Telmisartan/Amlodipine	44/7.1.3/0860	
	Bayer (Pty) Ltd	Ciprobay 250mg	Ciprofloxacin	
Ciprobay 500mg		Ciprofloxacin	U/20.1.1/127	
Ciprobay 750mg		Ciprofloxacin	U/20.1.1/128	
Ciprobay IV		Ciprofloxacin	Y/20.1.1/311	
Ciprobay IV Flexibag		Ciprofloxacin	32/20.1.1/0574	
Ciprobay Suspension 5%		Ciprofloxacin	31/20.1.1/0111	
Ciprobay Suspension 10%		Ciprofloxacin	31/20.1.1/0112	
Ciprobay XR500		Ciprofloxacin	37/20.1.1/0250	
Ciprobay XR1000		Ciprofloxacin	38/20.1.1/0024	
Avelon		Moxifloxacin	34/20.1.1/0008	
Avelon IV		Moxifloxacin	36/20.1.1/0052	
Bayquin Tablets		Moxifloxacin	42/20.1.1/0594	
Bayquin IV		Moxifloxacin	42/20.1.1/0595	
Moxibay Tablets		Moxifloxacin	42/20.1.1/0593	
Moxibay IV		Moxifloxacin	42/20.1.1/0592	

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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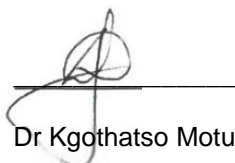
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Head: Ethics and Compliance & Responsible Pharmacist
Takeda (Pty) Ltd



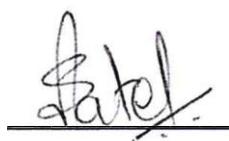
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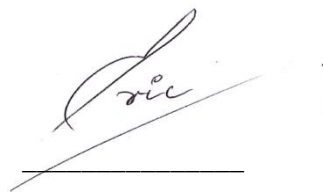
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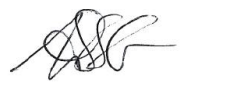
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