



IMPORTANT MEDICINE SAFETY INFORMATION

01 August 2019

Dear Healthcare Professional

Re: CONCOMITANT USE OF FLUOROQUINOLONES AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs) OR ANGIOTENSIN RECEPTOR BLOCKERS (ARBs): 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 Angiotensin-converting enzyme inhibitors (ACEIs) / Angiotensin receptor blockers (ARBs) and fluoroquinolones.

The Professional Information (PI) and Patient Information Leaflet (PIL) of fluoroquinolones, ACEIs and ARBs will be amended to reflect the above-mentioned 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 (ICSRs)¹.

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: https://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No1-2018.pdf?ua=1

- Among the 16 reports, assessment of individual case reports of five patients (cases 12-16) indicated a more likely alternative reason for AKI than a nephrotoxic effect of ciprofloxacin with enalapril. Analysis of the 11 remaining cases indicated that in most patients, although clinical conditions and a number of medicines were likely to have increased the risk of AKI, 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.
- In the literature analysis, presented in the publication SIGNAL April 2017² from the Uppsala Monitoring Centre, a nested case-control study in older men³, demonstrated a 2-fold greater 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.

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

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
Abex Pharmaceutica (Pty) Ltd Suite C Rubenstein Ridge, 617 Rubenstein Drive, Moreleta Park, 0181	Hytenza 50 (Film-coated tablets)	Losartan	43/7.1.3/0804	Lindie Marx Tel: +27 12 997 6974 Fax: +27 86 618 9511 E-mail: lmrx@abexpharm.com
	Hytenza 100 (Film-coated tablets)	Losartan	43/7.1.3/0805	
	Hytenza Co 50/12,5 (Film-coated tablets)	Losartan/ Hydrochlorothiazide	43/7.1.3/0806	
	Hytenza Co 100/25 (Film-coated tablets)	Losartan/ Hydrochlorothiazide	43/7.1.3/0807	
Accord Healthcare (Pty) Ltd Building 2, Tuscany Office Park, 6 Coombe Place, Rivonia, Johannesburg	Losaar Plus 50/12,5	Losartan/ Hydrochlorothiazide	42/7.1.3/0325	Reshlan Nagoor Tel: +27 11 234 5701/2 Fax: +27 11 234 5700 Email: reshlan.nagoor@accordhealth.co.za
	Losaar Plus 100/25	Losartan/ Hydrochlorothiazide	42/7.1.3/0326	

² Savage R: Ciprofloxacin, Enalapril and Acute Kidney Injury: Strengthening of a Drug Interaction Signal. SIGNAL April 2017, Uppsala Monitoring Centre and New Zealand.

³ Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JAC: Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ 2013; 185: E475-E482

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
Brimpharm SA (Pty) Limited 215 Main Road Claremont, 7708, Cape Town	Antosart 150 (Film-coated tablets)	Irbesartan	44/7.1.3/0910	Herlinde Kerremans van der Walt Tel: +27 21 671 6055 Fax: +27 21 671 8069 Email: pharmacist@brimpharm.com
	Antosart 300 (Film-coated tablets)	Irbesartan	44/7.1.3/0911	
Forrester Pharma (Pty) Ltd 13 Paita Street, Rosen Heights, Rosen Park, Bellville, 7530 Cape Town	Valduo 5/160 (Film-coated tablets)	Amlodipine/ Valsartan	51/7.1.3/0068	Fatima Booysen Tel: 021 943 0600 Fax: 021 914 2239 E-mail: info@forresterpharma.com or fatima.booyesen@forresterpharma.com
	Valduo 10/160 (Film-coated tablets)	Amlodipine/ Valsartan	51/7.1.3/0069	
LeBasi Pharmaceuticals CC Jankra Building, 3 O.R. Tambo Street, Potchefstroom, 2531	Jubitan 150 mg	Irbesartan	46/7.1.3/0124	Rudi Oliver Tel: +27 87 551 2972 Fax: +27 87 551 2973 E-mail: info@lebasi.co.za
	Jubitan 300 mg	Irbesartan	46/7.1.3/0125	
	Arbilo 50	Losartan	46/7.1.3/0980	
	Arbilo 100	Losartan	46/7.1.3/0981	
	Valheft 40	Valsartan	46/7.1.3/0743	
	Valheft 80	Valsartan	46/7.1.3/0744	
	Valheft 160	Valsartan	46/7.1.3/0745	
	Levojub 250	Levofloxacin	46/20.1.1/0977	
Levojub 500	Levofloxacin	46/20.1.1/0978		
Unichem SA (Pty) Ltd San Domenico Ground Floor, Unit G4, 10 Church Street, Durbanville, 7551, Cape Town	Renicard 50 mg	Losartan	A39/7.1.3/0580	Michelle Vivier Tel: +27 21 531 0436 Fax: +27 86 552 2777 E-mail: pharmacist@unichemsa.co.za

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



Lindie Marx
Responsible Pharmacist
Abex Pharmaceutica (Pty) Ltd



Reshlan Nagoor
Responsible Pharmacist
Accord Healthcare (Pty) Ltd



Herlinde Kerremans van der Walt
Deputy Responsible Pharmacist
Brimpharm SA (Pty) Limited



Fatima Booyen
Responsible Pharmacist
Forrester Pharma (Pty) Ltd



Rudi Oliver
Responsible Pharmacist
LeBasi Pharmaceuticals CC



Michelle Vivier
Responsible Pharmacist
Unichem SA (Pty) Ltd