IMPORTANT MEDICINE SAFETY INFORMATION

31 July 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 Angiotensin Converting Enzyme Inhibitors (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 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.intlmedicines/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, Etminan M, Brophy JM, Hartzema* AG, *Delaney JAG: Risk of acute kidney injury associated with the use offluoroquinolones. 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
sanofi-aventis south africa (pty) ltd	Levofloxacin Winthrop 500 (tablet)	A40/20.1.1/0310	500,0 mg levofloxacin per tablet	Tel: 082 828 0291 Fax: 086 686 3635 or 011 256 3721 Email: za.drugsafety@sanofi.com
	Levofloxacin Winthrop 750 (tablet)	43/20.1.1/1058	750,0 mg levofloxacin per tablet	
	Levofloxacin Winthrop I.V. 500 (injection)	A39/20.1.1/0578	500,0 mg levofloxacin per 100,0 ml vial	
	Levofloxacin Winthrop I.V. 750 (injection)	43/20.1.1/1059	750,0 mg levofloxacin per 150,0 ml vial	
	Tri-Plen (tablet)	31/7.1/0677	2,5 mg felodipine and 2,5 mg ramipril per tablet	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Tri-Plen Forte (tablet)	31/7.1/0678	5,0 mg felodipine and 5,0 mg ramipril per tablet	
	Rami Block 2,5/2,5 (tablet)	A38/7.1/0655	2,5 mg felodipine and 2,5 mg ramipril per tablet	
	Rami Block 5/5 (tablet)	A38/7.1/0654	5,0 mg felodipine and 5,0 mg ramipril per tablet	
	Ramiwin 2,5 mg (capsule)	W/7.1.3/233	2,5 mg ramipril per capsule	
	Ramiwin 5 mg (capsule)	W/7.1.3/234	5,0 mg ramipril per capsule	
	Tritace 10 mg (capsule)	W/7.1.3/235	10,0 mg ramipril per capsule	
	Tritace 2,5 mg Tablets (tablet)	31/7.1.3/0666	2,5 mg ramipril per tablet	
	Tritace 5 mg Tablets (tablet)	31/7.1.3/0667	5,0 mg ramipril per tablet	
	Tritace Plus 10/12.5 mg (tablet)	43/7.1/1130	10 mg ramipril and 12,5 mg HCTZ per tablet	
	Co Ramiwin 10/12.5 mg	44/7.1/0615	10 mg ramipril and 12,5 mg HCTZ per tablet	
	Co Ramiwin 2.5/12.5 mg (tablet)	44/7.1/0612	2,5 mg ramipril and 12,5 mg HCTZ per tablet	
	Co Ramiwin 5/12.5 mg (tablet)	44/7.1/0613	5 mg ramipril and 12,5 mg HCTZ per tablet	
	Aprovel 150 mg	31/7.1.3/0633	150 mg irbesartan per tablet	
	Irbewin 150	A40/7.1.3/0288	150 mg irbesartan per tablet	
	Aprovel 300 mg	31/7.1.3/0634	300 mg irbesartan per tablet	
	Irbewin 300	A40/7.1.3/0289	300 mg irbesartan per tablet	
	CoAprovel 150/12.5	33/7.1.3/0324	150 mg irbesartan and 12,5 mg HCTZ per tablet	
	Co-Irbewin 150/12.5	A40/7.1.3/0290	150 mg irbesartan and 12,5 mg HCTZ per tablet	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
			12,5 mg HCTZ per tablet	
	CoAprovel 300/12.5	33/7.1.3/0325	300 mg irbesartan and 12,5 mg HCTZ per tablet	
	Co-Irbewin 300/12.5	A40/7.1.3/0287	300 mg irbesartan and 12,5 mg HCTZ per tablet	
	Aterwin 8 mg	48/7.1.3/0412	8 mg candesartan cilexetil per tablet	
	Aterwin 16 mg	48/7.1.3/0413	16 mg candesartan cilexetil per tablet	
	Aterwin 32 mg	48/7.1.3/0414	32 mg candesartan cilexetil per tablet	

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 National Adverse Drug Event Monitoring Centre at Tel: 021 4471618 or Fax 021 448 6181.

Yours faithfully

Graeme James
Responsible Pharmacist
sanofi-aventis south africa (pty) ltd