

## **IMPORTANT MEDICINE SAFETY INFORMATION**

25 September 2019

Dear Healthcare Professional

**RE: FLUOROQUINOLONES AND ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS: ACUTE KIDNEY INJURY (AKI) ASSOCIATED WITH CONCOMITANT USE, ESPECIALLY IN INDIVIDUALS WITH MODERATE TO SEVERE RENAL IMPAIRMENT AND ELDERLY PATIENTS.**

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), Novartis SA (Pty) Ltd 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  $\leq 30$  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)<sup>1</sup>.
- 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<sup>2</sup> from the Uppsala Monitoring Centre; a nested case-control study in older men<sup>3</sup>, 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-PharmaceuticalsNewsletter No1-2018 .pdf?ua=1](http://www.who.int/medicines/publications/WHO-PharmaceuticalsNewsletter%20No1-2018.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 JAG: Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ 2013: 185: E475-E482*

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

Novartis SA (Pty) Ltd	Diovan 40	Valsartan 40	36/7.1.3/0382	Kumeshnie Padayachee Responsible Pharmacist Kumeshnie.padayachee@novartis.com
	Diovan 80	Valsartan 80	36/7.1.3/0034	
	Tareg 80	Valsartan 80	36/7.1.3/0067	Darren Katzman Director: Medical & Chief Scientific Officer (CSO) Darren.katzman@novartis.com
	Migroben 80	Valsartan 80	43/7.1.3/0032	
	Diovan 160	Valsartan 160	36/7.1.3/0035	
	Tareg 160	Valsartan 160	36/7.1.3/0068	
	Migroben 160	Valsartan 160	43/7.1.3/0033	Lesego Mabiletsa Patient Safety Country Head Lesego.mabiletsa@novartis.com
	Diovan 320	Valsartan 320	40/7.1.3/0542	
	Migroben 320	Valsartan 320	43/7.1.3/0523	patientsafety.sacg@novartis.com
	Co-Diovan 160/12.5 mg	Valsartan 160 /Hydrochlorothiazide 12.5 mg	34/7.1.3/0441	
	Co-Tareg 160/12.5 mg	Valsartan 160 /Hydrochlorothiazide 12.5 mg	41/7.1.3/0743	
	Co-Diovan 160 Plus	Valsartan 160 /Hydrochlorothiazide 25 mg	37/7.1.3/0225	
	Co-Migroben 160/25 mg	Valsartan 160 /Hydrochlorothiazide 25 mg	43/7.1.3/0085	
	Co-Tareg Plus 160/25 mg	Valsartan 160 /Hydrochlorothiazide 25 mg	41/7.1.3/0744	
	Co-Diovan 320/12.5 mg	Valsartan 320 /Hydrochlorothiazide 12.5 mg	41/7.1.3/0147	
	Co-Diovan 320/25 mg	Valsartan 320 /Hydrochlorothiazide 25 mg	41/7.1.3/0148	
	Co-Diovan 80/12.5 mg	Valsartan 80 /Hydrochlorothiazide 12.5 mg	32/7.1.3/0336	
	Co-Migroben 80/12.5 mg	Valsartan 80 /Hydrochlorothiazide 12.5 mg	43/7.1.3/0083	
	Co-Tareg 80/12.5 mg	Valsartan 80 /Hydrochlorothiazide 12.5 mg	35/7.1.3/0276	
	Exforge 5/80 mg	Amlodipine 5/ Valsartan 80 mg	41/7.1.3/0290	
Exforge 5/160 mg	Amlodipine 5/	41/7.1.3/0291		

		Valsartan 160 mg		
	Copalia 5/160 mg	Amlodipine 5/ Valsartan 160 mg	45/7.1.3/0850	
	Exforge 10/160 mg	Amlodipine 10/ Valsartan 160 mg	41/7.1.3/0292	
	Copalia 10/160 mg	Amlodipine 10/ Valsartan 160 mg	45/7.1.3/0851	
	Exforge 5/320 mg	Amlodipine 5/ Valsartan 320 mg	41/7.1.3/0770	
	Exforge 10/320 mg	Amlodipine 10/ Valsartan 320 mg	41/7.1.3/0771	
	Co-Exforge 10/160/12.5 mg	Amlodipine 10/ Valsartan 160 /Hydrochlorothiazide 12.5 mg	44/7.1.3/0077	
	Co-Exforge 10/160/25 mg	Amlodipine 10/ Valsartan 160 /Hydrochlorothiazide 25 mg	44/7.1.3/0078	
	Co-Exforge 10/320/25 mg	Amlodipine 10/ Valsartan 320 /Hydrochlorothiazide 25 mg	44/7.1.3/0079	
	Co-Exforge 5/160/12.5 mg	Amlodipine 5/ Valsartan 160 /Hydrochlorothiazide 12.5 mg	44/7.1.3/0075	
	Co-Exforge 5/160/25 mg	Amlodipine 5/ Valsartan 160 /Hydrochlorothiazide 25 mg	44/7.1.3/0076	
	Entresto 50 mg	Sacubitril valsartan sodium hydrate 50 mg	50/7.6/1016	
	Entresto 100 mg	Sacubitril valsartan sodium hydrate 100 mg	50/7.6/1017	
	Entresto 200 mg	Sacubitril valsartan sodium hydrate 200 mg	50/7.6/1018	
	Vymada 50 mg	Sacubitril valsartan sodium hydrate 50 mg	50/7.6/1019	
	Vymada 100 mg	Sacubitril valsartan sodium hydrate 100 mg	50/7.6/1020	
	Vymada 200 mg	Sacubitril valsartan sodium hydrate 200 mg	50/7.6/1021	

Healthcare Professionals should report all suspected adverse events associated with all ACE inhibitors/ARBs 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](mailto:adr@sahpra.org.za) or the National Adverse Drug Event Monitoring Centre at Tel: 021 4471618 or Fax 0214486181.

Yours faithfully



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