NOVARTIS

**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)[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/p ublications/WHO-PharmaceuticalsNewsletter 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 of fluoroquinolones. CMAJ 2013: 185: E475-E482*

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

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|---|---|---|---|---|
| Novartis SA (Pty) Ltd | Diovan 40 | Valsartan 40 | 36/7.1.3/0382 | Kumeshnie Padayachee<br>Responsible Pharmacist<br>Kumeshnie.padayachee@novartis.com<br><br>Darren Katzman<br>Director: Medical & Chief Scientific Officer (CSO)<br>Darren.katzman@novartis.com<br><br>Lesego Mabiletsa<br>Patient Safety Country Head<br>Lesego.mabiletsa@novartis.com<br><br>patientsafety.sacg@novartis.com |
| | Diovan 80 | Valsartan 80 | 36/7.1.3/0034 | |
| | Tareg 80 | Valsartan 80 | 36/7.1.3/0067 | |
| | 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 | |
| | Diovan 320 | Valsartan 320 | 40/7.1.3/0542 | |
| | Migroben 320 | Valsartan 320 | 43/7.1.3/0523 | |
| | 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 | |

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|---|---|---|---|---|
| | | 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 or the National Adverse Drug Event Monitoring Centre at Tel: 021 4471618 or Fax 0214486181.

Yours faithfully

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Responsible Pharmacist

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Lesego Mabiletsa
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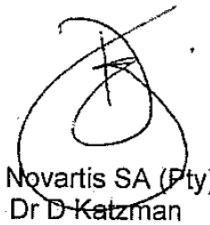

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Dr D Katzman
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