

## IMPORTANT MEDICINE SAFETY INFORMATION

29 May 2020

Dear Healthcare Professional

### RE: FLUOROQUINOLONE ANTIBIOTICS – RISK OF MITRAL AND AORTIC REGURGITATION ASSOCIATED WITH THE USE OF ORAL AND INJECTABLE FLUOROQUINOLONES

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the companies listed below would like to inform you about the risk of mitral and aortic regurgitation that should be taken into consideration when prescribing oral fluoroquinolone antibiotics.

The Professional Information (PI) and Patient Information Leaflet (PIL) of the fluoroquinolones will be updated accordingly.

#### **Background to safety concern**

The safety concern is as a result of the article ‘Oral fluoroquinolones and risk of mitral and aortic regurgitation’ as published in the Journal of the American College of Cardiology.

The authors, Etminan *et al*, conducted a disproportionality analysis using data from the FDA Adverse Events Reporting System (FAERS) database to probe whether the risk of developing aortic and/or mitral regurgitation is higher with oral and injectable fluoroquinolone use compared to non-fluoroquinolone use.

The study results showed that there is some evidence, although inconclusive, of a possible increased risk for patients to develop mitral valve and/or aortic valve regurgitation (left sided heart valves) while on treatment with oral fluoroquinolones. The increased risk continues until about 60 days after completion of treatment (an association between current and recent use of oral fluoroquinolones and the development of aortic/mitral valve regurgitation). The risk also appeared to be the highest in current fluoroquinolone users followed by recent fluoroquinolone users.

#### **Based on the above findings it is recommended that:**

- A thorough cardiovascular examination, including an echocardiogram (ECG), should be performed, before oral or injectable fluoroquinolones are prescribed.
- Fluoroquinolones should not be prescribed to patients with mitral valve and/or aortic valve regurgitation, unless no safer alternative antibiotic is available, has failed or is not well tolerated.

Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality issues to SAHPRA via the eReporting link available on the SAHPRA website ([www.sahpra.org.za](http://www.sahpra.org.za)). Alternatively, please complete the ADR reporting form accessible via the SAHPRA website at <https://www.sahpra.org.za/documents/12e54dcaADRForms.pdf> and email it to [adr@sahpra.org.za](mailto:adr@sahpra.org.za) or fax to (021) 448 6181. For more information on ADR reporting, please call the SAHPRA vigilance unit on (012) 842 7609/10 or National Adverse Events Monitoring Centre (NADEMC) on (021) 447 1618.

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
<b>Cipla Medpro (Pty) Ltd</b>	Mofloxx 400	Moxifloxacin	44/20.1.1/1063	<b>Tel:</b> 021 943 4200 <b>Fax:</b> 021 914 1587 <b>Email:</b> <a href="mailto:drugsafetysa@Cipla.com">drugsafetysa@Cipla.com</a>
	Tavaloxx 250	Levofloxacin	41/20.1.1/0007	
	Tavaloxx 500	Levofloxacin	41/20.1.1/0008	
	Tavaloxx 750	Levofloxacin	41/20.1.1/0009	
	Utin-400	Norfloxacin	31/20.1.1/0517	
	Ciploxx 250	Ciprofloxacin	36/20.1.1/0376	
	Ciploxx 500	Ciprofloxacin	36/20.1.1/0377	
<b>Adcock Ingram Critical Care (Pty) Ltd</b>	Adco Ciprofloxacin 2 mg/ml	Ciprofloxacin	39/20.1.1/0646	<b>Tel:</b> 011 635 0134 <b>Fax:</b> 086 553 0128 Email: <a href="mailto:adcock.aereports@adcock.com">adcock.aereports@adcock.com</a>
<b>Ethicare</b>	Tafloc 400 mg	Ofloxacin	35/20.1.1/0175	<b>Tel:</b> 0800 118 088, <b>Fax:</b> 011 239 6306, <b>Email:</b> <a href="mailto:drugsafety@aspenpharma.com">drugsafety@aspenpharma.com</a>
	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	
<b>Pharma Dynamics (Pty) Ltd</b>	Dynafloc 500	Ciprofloxacin	34/20.1.1/0405	<b>Tel:</b> 021 707 7000; <b>Fax:</b> 021 702 0533 <b>Email:</b> <a href="mailto:pharmacovigilance@pharmadynamics.co.za">pharmacovigilance@pharmadynamics.co.za</a> & <a href="mailto:p.vanvuuren@pharmadynamics.co.za">p.vanvuuren@pharmadynamics.co.za</a>
	Levonic IV 500	Levofloxacin	42/20.1.1/0998	
<b>Actavis Pharma (Pty) Ltd, a subsidiary of Teva Pharmaceutical Industries</b>	Ciprol 250	Ciprofloxacin	37/20.1.1/0573	<b>Tel:</b> 011 055 0200 <b>Fax:</b> 011 388 2688 <b>Email:</b> <a href="mailto:Safety.South-Africa@teva.co.il">Safety.South-Africa@teva.co.il</a>
	Ciprol 500	Ciprofloxacin	37/20.1.1/0574	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
Zydus Healthcare SA (Pty) Ltd	Zybact 250 mg	Levofloxacin 250 mg	44/20.1.1/0249	<b>Tel:</b> 012 748 6400 <b>Email:</b> <a href="mailto:medicinesafety@zydus.co.za">medicinesafety@zydus.co.za</a>
	Zybact 500 mg	Levofloxacin 500 mg	44/20.1.1/0250	
Austell Laboratories (Pty) Ltd	Austell Levofloxacin 250 mg	Levofloxacin hemihydrate	41/20.1.1/1018	<b>Tel:</b> 011 611 1400 <b>Fax:</b> 086 455 0101 <b>Email:</b> <a href="mailto:smahomed@austell.co.za">smahomed@austell.co.za</a>
	Austell Levofloxacin 500 mg	Levofloxacin hemihydrate	41/20.1.1/1019	
	Levostel 250	Levofloxacin hemihydrate	41/20.1.1/1022	
	Levostel 500	Levofloxacin hemihydrate	41/20.1.1/1023	
	Ausvanic 250	Levofloxacin hemihydrate	41/20.1.1/1020	
	Ausvanic 500	Levofloxacin hemihydrate	41/20.1.1/1021	
	Austell Ciprofloxacin 250 mg	Ciprofloxacin hydrochloride	38/20.1.1/0011	
	Austell Ciprofloxacin 500 mg	Ciprofloxacin hydrochloride	38/20.1.1/0012	
	Austell Ciprofloxacin 750 mg	Ciprofloxacin hydrochloride	37/20.1.1/0354	
	Floqin IV 2 mg/ml	Ciprofloxacin lactate	50/20.1.1/1035	
	Austell Ofloxacin 200 mg	Ofloxacin	A39/20.1.1/0149	
	Austell Ofloxacin 400 mg	Ofloxacin	A39/20.1.10150	
	Austell Moxifloxacin IV 400 mg/250 ml	Moxifloxacin hydrochloride	50/20.1.1/0434	
	Avoxa 400 mg	Moxifloxacin hydrochloride	46/20.1.1/0643	
Ranbaxy (SA) (Pty) Ltd	Tavanic 500 Tablets	Levofloxacin	32/20.1.1/0124	<b>Tel:</b> 012 643 2033/ 011 495 0117 <b>Fax:</b> 0126432001/3 <b>Email:</b> <a href="mailto:susan.heritage@sunpharma.com">susan.heritage@sunpharma.com</a> <a href="mailto:Barryjames.lewis@sunpharma.com">Barryjames.lewis@sunpharma.com</a>
	Tavanic 250 Tablets	Levofloxacin	32/20.1.1/0123	
	Tavanic I.V. 250	Levofloxacin	34/20.1.1/0002	
Ranbaxy Pharmaceuticals (Pty) Ltd	Tavanic I.V. 750	Levofloxacin	43/20.1.1/0948	<b>Tel:</b> 011 495 0181/011 495 0117 <b>Fax:</b> 011 495 0150
	Tavanic I.V 500	Levofloxacin	32/20.1.1/0125	
	Tavanic 750 Tablets	Levofloxacin	43/20.1.1/0947	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Floxin	Norfloxacin 400 mg	32/20.1.1/0377	<b>Email:</b> <a href="mailto:Geeta.ghela@sunpharma.com">Geeta.ghela@sunpharma.com</a> <a href="mailto:Barryjames.lewis@sunpharma.com">Barryjames.lewis@sunpharma.com</a>
	Cifran 250 Tablets	Ciprofloxacin	33/20.1.1/0365	
	Cifran 500 Tablets	Ciprofloxacin	33/20.1.1/0366	
	Avebact 400	Moxifloxacin	41/20.1.1/0778	
<b>LeBasi Pharmaceuticals CC</b>	Levojub 250	Levofloxacin	46/20.1.1/0977	<b>Tel:</b> 087 551 2972 <b>Fax:</b> 087 551 2973 <b>Email:</b> <a href="mailto:info@lebasi.co.za">info@lebasi.co.za</a>
	Levojub 500	Levofloxacin	46/20.1.1/0978	
<b>Dr Reddy's Laboratories (Pty) Ltd</b>	Cifloc 250	Ciprofloxacin 250mg	34/20.1.1/0308	<b>Tel:</b> 011 324 2100 <b>Email:</b> <a href="mailto:AdverseEvents.SA@drreddys.com">AdverseEvents.SA@drreddys.com</a>
	Cifloc 500	Ciprofloxacin 500mg	34/20.1.1/0309	
	DRL Moxifloxacin 400	Moxifloxacin 400mg	42/20.1.1/0442	
<b>Macleods Pharmaceuticals SA</b>	Lonxave 400	Moxifloxacin 400 mg	48/20.1.1/0024	<b>Tel:</b> 011 682 1169 <b>Cell:</b> 082 450 6204 <b>Fax:</b> 086 433 5398 <b>Email:</b> <a href="mailto:rgosai@macleodspharma.com">rgosai@macleodspharma.com</a>
	Avrokel 250 mg (previously Macleods Levofloxacin 250 mg)	Levofloxacin 250 mg	45/20.1.1/0684	
	Avrokel 500 mg (previously Macleods Levofloxacin 500 mg)	Levofloxacin 500 mg	45/20.1.1/0685	
<b>Aurobindo Pharma (Pty) Ltd</b>	Loxip 500	Ciprofloxacin 500mg	41/20.1.1/1053	<b>Tel:</b> 011 867 9104 <b>Email:</b> <a href="mailto:pv.za@aurobindo.com">pv.za@aurobindo.com</a>
<b>Xixia Pharmaceuticals (Pty) Ltd</b> [Marketed by Mylan (Pty) Ltd]	Mylan Levofloxacin 250 mg (Film-coated tablets)	Levofloxacin hemihydrate 256,23 mg equivalent to 250 mg levofloxacin	43/20.1.1/0841	<b>Tel:</b> 071 281 2503 <b>Email:</b> <a href="mailto:medinfosa@mylan.com">medinfosa@mylan.com</a>
	Mylan Levofloxacin 500 mg (Film-coated tablets)	Levofloxacin hemihydrate 512,46 mg equivalent to 500 mg levofloxacin	43/20.1.1/0842	
<b>Mylan (Pty) Ltd</b>	Ciprogen IV 200 mg/100 ml (Solution)	Ciprofloxacin 2 mg/ml	A40/20.1.1/0618	<b>Tel:</b> 071 281 2503 <b>Email:</b> <a href="mailto:medinfosa@mylan.com">medinfosa@mylan.com</a>
<b>Fresenius Kabi South Africa (Pty) Ltd</b>	Ciprofloxacin Fresenius 2 mg/ml 100 ml	Ciprofloxacin hydrogen sulphate	45/20.1.1/0798	<b>Tel:</b> 011 545 0000 <b>Email:</b>

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Ciprofloxacin Fresenius 2 mg/ml 200 ml	Ciprofloxacin hydrogen sulphate	45/20.1.1/0799	<a href="mailto:safety.fksa@fresenius-kabi.com">safety.fksa@fresenius-kabi.com</a>
	Levofloxacin 100ml	Levofloxacin hemihydrate equivalent to levofloxacin.	45/20.1.1/0139	
Sandoz	Cipro-Hexal 250	Ciprofloxacin (Hydrochloride)	36/20.1.1/0170	<b>Tel:</b> +27 11 347 6600 <b>Fax:</b> +27 11 929 2262 <b>Email:</b> <a href="mailto:patientsafety.sacg@novartis.com">patientsafety.sacg@novartis.com</a>
	Cipro-Hexal 500	Ciprofloxacin (Hydrochloride)	36/20.1.1/0171	
	Cipro-Hexal 750	Ciprofloxacin (Hydrochloride)	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	
Novagen Pharma (Pty) Ltd	Flopro 500 mg tablets	Ciprofloxacin 500 mg	45/20.1.1/0199	<b>Tel:</b> +27 12 345 3175 <b>Fax:</b> +27 86 665 7070 <b>Email:</b> <a href="mailto:telanie@novagenpharma.co.za">telanie@novagenpharma.co.za</a> <a href="mailto:elizma@novagenpharma.co.za">elizma@novagenpharma.co.za</a>
Sanofi-Aventis South Africa (Pty) Ltd	Levofloxacin Winthrop 500	Levofloxacin hemihydrate equivalent to 500 mg levofloxacin	A40/20.1.1/0310	<b>Tel:</b> +27 11 256 3700 <b>Email:</b> <a href="mailto:za.drugsafety@sanofi.com">za.drugsafety@sanofi.com</a>
	Levofloxacin Winthrop 750	Levofloxacin hemihydrate equivalent to 750 mg levofloxacin	43/20.1.1/1058	
	Levofloxacin Winthrop I.V. 500	Levofloxacin hemihydrate equivalent to 500 mg levofloxacin	A39/20.1.1/0578	
	Levofloxacin Winthrop I.V. 750	Levofloxacin hemihydrate equivalent to 750 mg levofloxacin	43/20.1.1/1059	

Yours faithfully,

<p>Dr Nic de Jongh Vice President – Chief Scientific Officer <b>Cipla Medpro (Pty) Ltd</b></p>  <p><b>Signature:</b></p>	<p>Nikola Whelan Head Group Pharmaceutical Affairs and Responsible Pharmacist <b>Ethicare</b></p>  <p><b>Signature:</b></p>	<p>Petra van Vuuren Deputy Responsible Pharmacist <b>Pharmadynamics (Pty) Ltd</b></p>  <p><b>Signature:</b></p>
<p>Emily Ramalingham Responsible Pharmacist <b>Actavis Pharma (Pty) Ltd</b></p>  <p><b>Signature:</b></p>	<p>Madhu B Swarna Responsible Pharmacist <b>Zydus Healthcare SA (Pty) Ltd</b></p>  <p><b>Signature:</b></p>	<p>Susan Heritage Responsible Pharmacist <b>Ranbaxy (SA) (Pty) Ltd</b></p>  <p><b>Signature:</b></p>
<p>Geeta Ghela QA Head &amp; Responsible Pharmacist <b>Ranbaxy Pharmaceuticals (Pty) Ltd</b></p>  <p><b>Signature:</b></p>	<p>Rudi Oliver Responsible Pharmacist <b>LeBasi Pharmaceuticals cc</b></p>  <p><b>Signature:</b></p>	<p>Herman Beyers Responsible Pharmacist <b>Dr Reddy's Laboratories (Pty) Ltd</b></p>  <p><b>Signature</b></p>
<p>Rashmi Gosai Deputy Responsible Pharmacist <b>Macleods Pharmaceuticals SA</b></p>  <p><b>Signature:</b></p>	<p>Shalini Naidoo Responsible Pharmacist <b>Aurobindo Pharma (Pty) Ltd</b></p>  <p><b>Signature:</b></p>	<p>Mogini Nadasan Responsible Pharmacist <b>Xixia Pharmaceuticals (Pty) Ltd</b></p>  <p><b>Signature:</b></p>

<p>Ansie Savrda Responsible Pharmacist <b>Mylan (Pty) Ltd</b></p> <p><i>A Savrda</i></p> <p><b>Signature:</b></p>	<p>Shehnaz Mahomed Responsible Pharmacist/Head of Regulatory Affairs <b>Austell Laboratories (Pty) Ltd</b></p> <p><i>Shehnaz Mahomed</i></p> <p><b>Signature:</b></p>	<p>Lucelle Iyer Head of QA, RA and Compliance (Responsible Pharmacist) <b>Adcock Ingram Critical Care (Pty) Ltd</b></p> <p><i>Lucelle Iyer</i></p> <p><b>Signature:</b></p>
<p>Sharon Davis Head of Quality/ Responsible Pharmacist <b>Fresenius Kabi South Africa (Pty) Ltd</b></p> <p><i>Sharon Davis</i></p> <p><b>Signature:</b></p>	<p>Telanie Venter Responsible Pharmacist / Pharmacovigilance Officer <b>Novagen Pharma (Pty) Ltd</b></p> <p><i>Telanie Venter</i></p> <p><b>Signature:</b></p>	<p>Dewald Killian Responsible Pharmacist <b>Sandoz SA (Pty) Ltd</b></p> <p>pp <i>Dewald Killian</i></p> <p><b>Signature:</b></p>
<p>Graeme James Head of Regulatory/ Responsible Pharmacist <b>Sanofi-Aventis South Africa (Pty) Ltd</b></p> <p><i>Graeme James</i></p> <p><b>Signature:</b></p>		

**References:**

1. Etminan et al. 2019. Oral fluoroquinolones and risk of mitral and aortic regurgitation. *Journal of American College of Cardiology*. Vol 74(11), pg1444-50.