

Direct Healthcare Professional Communication

Systemic and inhaled fluoroquinolones: risk of heart valve regurgitation/incompetence

Dear Healthcare professional,

Accord Healthcare Limited, Actavis Group PTC ehf, Anfarm Hellas S.A., Bayer Limited, BIAL – Portela & C^a, S.A., Central Procurement & Supplies Unit, Chiesi Farmaceutici S.p.A, Clonmel Healthcare Limited, COOPER Pharmaceuticals S.A., Delorbis Pharmaceuticals Limited, Fresenius Kabi Italia S.r.l., Healthhouse Pharma Ltd, Ibigen S.r.L, KRKA, d.d., Novo mesto, Medical Logistics Ltd, Medochemie Limited, NeoFarma Pharmaceuticals Limited, Noridem Enterprises Ltd, Norma Hellas S.A., PIAM Farmaceutici S.p.A., Remedica Limited, Rowex Ltd, S.C. AC Helcor Pharma S.R.L., Sanofi S.r.l., Villerton Invest S.A. in agreement with the European Medicines Agency and the Malta Medicines Authority would like to inform you of the risk of heart valve regurgitation/incompetence associated with fluoroquinolones for systemic and inhalation use.

Summary

- **Systemic and inhaled fluoroquinolones may increase the risk of heart valve regurgitation/incompetence**
- **Conditions predisposing to heart valve regurgitation/incompetence include congenital or pre-existing heart valve disease, connective tissue disorders (for example Marfan syndrome or Ehlers-Danlos syndrome) Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis, and infective endocarditis**
- **In patients at risk for heart valve regurgitation/incompetence, systemic and inhaled fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options**
- **Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.**

Background on the safety concern

Fluoroquinolones are antibiotics approved in the European Union for the treatment of certain bacterial infections, including life-threatening ones. Because they can have serious and long-lasting side effects, their use is generally restricted to infections where it is considered inappropriate to use other antibiotics commonly recommended for these infections (risk subject to a Direct Healthcare Professional Communication circulated in April 2019. DHPC published by the Malta Medicines Authority can be retrieved from <http://www.medicinesauthority.gov.mt/dhpc>). Fluoroquinolones should only be used after carefully assessing its likely benefits and its risks including that of aortic aneurysm and dissection (risk subject to a Direct Healthcare Professional Communication circulated in October 2018. DHPC published by the Malta Medicines Authority can be retrieved from <http://www.medicinesauthority.gov.mt/dhpc>).

A recent epidemiological study [1] reported an about 2-fold increase in risk of mitral and aortic regurgitation in patients taking systemic fluoroquinolones compared with patients taking other antibiotics (amoxicillin or azithromycin).

Several medically confirmed cases of heart valve regurgitation/incompetence affecting any heart valve have been reported in patients receiving fluoroquinolones with probable or possible causal association. These data indicate that fluoroquinolones can cause heart valve regurgitation/incompetence.

Additionally, a laboratory study [2] reported that exposure to ciprofloxacin led to collagen degradation in aortic myofibroblasts cells donated from patients with aortopathy, including aortic regurgitation. This finding provides insight into how fluoroquinolone-associated degradation of connective tissue may be associated with heart valve regurgitation/incompetence. Collagen degradation has also been postulated for fluoroquinolone-associated disorders of tendons and the aorta.

Factors that increase the risk for heart valve regurgitation/incompetence include congenital or pre-existing heart valve disease, connective tissue disorders (for example Marfan syndrome or Ehlers-Danlos syndrome), Turner syndrome, Behçet's disease, hypertension, rheumatoid arthritis, and infective endocarditis.

In patients at risk for heart valve regurgitation/incompetence, systemic and inhaled fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic treatment options.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

References

[1] Etminan M, Sodhi M, Ganjizadeh-Zavareh S, Carleton B, Kezouh A, Brophy JM. Oral Fluoroquinolones and Risk of Mitral and Aortic Regurgitation. *J Am Coll Cardiol*. 2019 Sep 17;74(11):1444-1450

[2] Guzzardi DG, Teng G, Kang S, Geeraert PJ, Pattar SS, Svystonyuk DA, Belke DD, Fedak PWM. Induction of human aortic myofibroblast-mediated extracellular matrix dysregulation: A potential mechanism of fluoroquinolone-associated aortopathy. *J Thorac Cardiovasc Surg*. 2019 Jan;157(1):109-119.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with fluoroquinolone containing products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

Company contact point

Should you have any questions or require additional information, please call Medical Information at:

Company	Product Name	Email	Phone
Accord Healthcare Limited	Ciprofloxacin 250mg Film-Coated Tablets	medinfo@accord-healthcare.com	+44 (0)1271 385257
	Levofloxacin 250mg Film-coated Tablets		
	Levofloxacin 500mg Film-coated Tablets		
Actavis Group PTC ehf	Siprox 500mg film-coated tablets	PHVMALTA@actavis.com	+356 2367 9650 +30 211 880 5166
	Siprox 250mg film-coated tablets		
	Levoxa 250mg film-coated Tablets		
	Levoxa 500mg film-coated Tablets		
	Levofloxacin Solution for Infusion 5mg/ml (50ml vial)		
	Levofloxacin Solution for Infusion 5mg/ml (100ml vial)		
Anfarm Hellas S.A.	Aristin-C	phvigilance@anfarm.com	+30 2106831632 +30 6932331620
	Aristin-C		
	Aristin-C		
	Moxifloxacin Anfarm 400MG/250ML Solution for Infusion		
	Fluseminal		
Bayer Limited	Ciproxin 500mg Film-coated Tablets	pv@alfredgera.com	+356 21446205
	Ciproxin Solution for Infusion 200mg/100ml		
	Avelox 400mg film-coated Tablets		
	Avelox 400mg/250ml solution for infusion		
BIAL – Portela & C^ª, S.A.	UROFLOX, 400mg, film-coated Tablets	adrs@adc.com.mt	+356 22778116
Central Procurement & Supplies Unit	Ciprofloxacin Tablet, film coated 250mg	Info.cpsu@gov.mt	+356 25953302/3
	Levofloxacin 500mg Film-coated Tablets		
	Levofloxacin Tablet, film coated 500mg		
	Moxifloxacin 400mg film-coated Tablets		
	Moxifloxacin 400mg film-coated Tablets		

Company	Product Name	Email	Phone
Chiesi Farmaceutici S.p.A.	Quinsair 240 mg nebuliser solution	GlobalPV@chiesi.com	+39 05212791
Clonmel Healthcare Limited	Profloxin Tablet, film coated 250mg	medicalinformation@clonmel-health.ie	+353 52 6177777
	Profloxin Tablet, film coated 500mg		
COOPER Pharmaceuticals S.A.	Nafloxin 200mg/100ml Injectable Solution for Infusion	safety@zeincro.com	+30 210 3462108
		ntousi@koper.gr	+30 6972 093996
Delorbis Pharmaceuticals Limited	Viprolox 250mg Film coated tablets	safety@pharmassist.gr	+30 210 6561435
	Viprolox 500mg Film coated tablets		
	Floxaval 500mg Film-coated tablets		
Fresenius Kabi Italia S.r.l	Ciprofloxacin Kabi 200mg/100ml solution for infusion	paola.ragazzo@fresenius-kabi.com	+39 045 2053766
	Levofloxacin Solution for Infusion 5mg/ml	farmacovigilanza.fki@fresenius-kabi.com	+ 39 3489710480
Healthhouse Pharma Ltd	Levofloxacin Solution for Infusion 5mg/ml	ian.greenep@healthhousepharma.co.uk	+44 01420487501
	Levofloxacin Solution for Infusion 5mg/ml		
	Ciproxin 250 mg/5 mL granules and solvent for oral suspension		
	Moxifloxacin 400 mg film-coated tablets		
Ibigen S.r.L	Levofloxacin Ibigen Solution for Infusion 5mg/ml (50ml vial)	safety@drugsalesltd.com	+356 21419070/1/2
	Levofloxacin Ibigen Solution for Infusion 5mg/ml (100ml vial)		
KRKA, d.d., Novomesto	Ciprinol 250mg film-coated Tablets	pharmacovigilance@krka.biz	+356 21447184
	Ciprinol 500mg film-coated Tablets		
Medical Logistics Ltd	Ciprofloxacin Tablet, film coated 250mg	samantha@ml.com.mt julienne@ml.com.mt	+356 27559990
	Ciprofloxacin Tablet, film coated 500mg		
Medochemie Limited	Medociprin	Alex.fenech@europharma.com.mt	+356 23859239
	Medociprin		
	Amesol 500mg film-coated Tablets		
	ERELAN 400mg film-coated Tablet		

Company	Product Name	Email	Phone
NeoFarma Pharmaceuticals Limited	Ciprofloxacin Teva 250mg film-coated Tablets	rp@neofarma.com.mt pc@neofarma.com.mt	+356 99109494
	Ciprofloxacin Teva 500mg film-coated Tablets		
	Tavanic Coated Tablets 500mg		
Noridem Enterprises Ltd	Ciprofloxacin Solution for Infusion 2mg/ml	pv@demo.gr	+30 2108161802
	Levofloxacin Solution for Infusion 5mg/ml		
Norma Hellas S.A.	Revionorm Solution for Infusion 200mg/100ml	safety@pharmassist.gr savvas@normahellas.gr	+30 2106561435 +30 2105222282
PIAM Farmaceutici S.p.A.	TRISSIL 500mg film-coated tablets	aparis@prohealth.com.mt	+356 23385313
Remedica Limited	Zindolin 250mg Film-Coated Tablets	a.vasiliou@remedica.com.cy drugsafety@remedica.com.cy	+357 25 55 32 51 +357 25 55 30 00
	Trizolin 400 Tablet, film coated 400mg		
Rowex Ltd	Cifox Tablet, film coated 500mg	pv@rowa-pharma.ie	+353 (0)2750077
	Cifox Tablet, film coated 750mg		
S.C. AC Helcor Pharma S.R.L.	Ciprolen Tablet, film coated 250mg	office@achelcor.ro	+40 362- 401206
	Ciprolen Tablet, film coated 500mg		
Sanofi S.r.l.	Tavanic 500mg film-coated tablets	Informazioni.medicoscientifiche@sanofi.com PharmacovigilanceMalta@sanofi.com	+39 02 3939 4275 / 4716 / 4374
Villerton Invest S.A.	Ciprofloxacin 2mg/ml Solution for Infusion	safety@drugsalesltd.com	+356 21419070/1/2

Yours faithfully,

Post-Licensing Directorate

Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Accord Healthcare Limited, Actavis Group PTC ehf, Anfarm Hellas S.A., Bayer Limited, BIAL – Portela & C^a, S.A., Central Procurement & Supplies Unit, Chiesi Farmaceutici S.p.A., Clonmel Healthcare Limited, COOPER Pharmaceuticals S.A., Delorbis Pharmaceuticals Limited, Fresenius Kabi Italia S.r.l , Healthhouse Pharma Ltd, Ibigen S.r.L, KRKA, d.d., Novo mesto, Medical Logistics Ltd , Medochemie Limited, NeoFarma Pharmaceuticals Limited, Noridem Enterprises Ltd, Norma Hellas S.A., PIAM Farmaceutici S.p.A., Remedica Limited, Rowex Ltd, S.C. AC Helcor Pharma S.R.L., Sanofi S.r.l., Villerton Invest S.A.

