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Direct Healthcare Professional Communication

Systemic and inhaled fluoroquinolones: risk of aortic aneurysm and dissection

Dear healthcare professionals,

Accord Healthcare Limited, Actavis Group PTC ehf, Anfarm Hellas S.A., Bayer PLC, Beximco Pharma UK Ltd, Bial - Portela & C S.A., Chiesi Farmaceutici S.p.A., Claris Lifesciences UK Limited, Clonmel Healthcare Limited, COOPER S.A. Pharmaceuticals, Delorbis Pharmaceuticals Limited, DEMO S.A. Pharmaceutical Industry, Fresenius Kabi Italia S.r.l., Fresenius Kabi Limited, Ibigen S.r.l., KRKA, d. d., Novo Mesto, Medochemie Limited, Mylan S.A.S., Noridem Enterprises Ltd, Norma Hellas S.A., P & D Pharmaceuticals Limited, PIAM Farmaceutici S.p.A., Remedica Limited, Rowex Ltd, S.C. AC Helcor Pharma S.R.L., Sanofi Malta Limited, TAD Pharma GmbH, Villerton Invest S.A., in agreement with the European Medicines Agency and the Malta Medicines Authority would like to inform you of the addition of a new warning regarding risk of aortic aneurysm and dissection associated with fluoroquinolones for systemic and inhalation use.

Summary

- **Systemic and inhaled fluoroquinolones may increase the risk of aortic aneurysm and dissection, particularly in older people.**
- **In patients at risk for aortic aneurysm and dissection, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options.**
- **Conditions predisposing to aortic aneurysm and dissection include a family history of aneurysm disease, pre-existing aortic aneurysm or aortic dissection, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, and atherosclerosis.**
- **Patients should be advised about risk of aortic aneurysm and dissection and told to seek immediate medical attention in the emergency department in case of sudden severe abdominal, chest or back pain.**

Background on the safety concern

Fluoroquinolones are antibiotics approved in the European Union for the treatment of several bacterial infections, including life-threatening ones.

Data from epidemiologic and non-clinical studies indicate an increased risk of aortic aneurysm and dissection after treatment with fluoroquinolones.

The epidemiological studies [1-3] report an about 2-fold increase in risk of aortic aneurysm and dissection in patients taking systemic fluoroquinolones compared with patients taking no antibiotics or other antibiotics (amoxicillin); with older people being at higher risk.

A non-clinical study [4] reported that ciprofloxacin increases the susceptibility to aortic dissection and rupture in a mouse model. This finding is likely a class effect similar to fluoroquinolones being harmful to tendon tissue and thereby increasing the risk of tendon disorders.

Aortic aneurysm and dissection are rare events, occurring with an incidence of about 3–30 of 100,000 persons per year. Factors that increase the risk include family history of aneurysm disease, pre-existing aortic aneurysm or aortic dissection, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, and atherosclerosis.

Therefore, systemic or inhaled fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients at risk for aortic aneurysm and dissection.

Patients should be advised about this risk and told to seek immediate medical attention in case of sudden abdominal, chest or back pain.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with fluoroquinolones medicines in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

▼ Quinsair 240 mg nebuliser solution is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

References

- [1] Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open*. 2015 Nov 18; 5(11):e010077
- [2] Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, Chang SC. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med*. 2015 Nov;175(11):1839-47.
- [3] Pasternak B, Inghammar M and Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018; 360: k678.
- [4] LeMaire SA, Zhang L, Luo W, Ren P, Azares AR, Wang Y, Zhang C, Coselli JS, Shen YH. Effect of Ciprofloxacin on Susceptibility to Aortic Dissection and Rupture in Mice. *JAMA Surg*. 2018 Jul 25:e181804. [Epub ahead of print]

Company contact point

Company	Product name	Email	Phone
Accord Healthcare Limited	Ciprofloxacin 250mg Film-Coated Tablets Levofloxacin 250mg Film-coated Tablets Levofloxacin 500mg Film-coated Tablets	pkarmarkar@accord-healthcare.com	+44 0208 863 1427
Actavis Group PTC ehf	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) Siprox 250mg film coated tablets Siprox 500mg film coated tablets	PHVMALTA@actavis.com	+30 2118805156
Anfarm Hellas S.A.	Aristin-C Fluseminal	alex.fenech@euopharma.com.mt	+356 2385 9239
Bayer plc	Ciproxin 250mg Film-coated Tablets Ciproxin 500mg Film-coated Tablets Ciproxin Solution for Infusion 100mg/50ml Ciproxin Solution for Infusion 200mg/100ml Ciproxin Solution for Infusion 400mg/200ml Ciproxin 750mg Film-Coated Tablets Avelox 400mg film-coated Tablets Avelox 400mg/250ml solution for infusion	acurmi@alfredgera.com	+35621446205

Company	Product name	Email	Phone
Beximco Pharma UK Ltd	Levofloxacin Beximco Coated Tablets 250mg Levofloxacin Beximco Coated Tablets 500mg	isr@bpl.net	+880 2 58611001 ext 20624
Bial - Portela & C S.A.	UROFLOX, 400mg, film-coated Tablets	pharmacovigilance@bial.com	+351 22 986 61 53
Chiesi Farmaceutici S.p.A.	Quinsair 240 mg nebuliser solution	GlobalPV@chiesi.com	+39 0521 279 701
Claris Lifesciences UK Limited	Ciprofloxacin 2mg/ml Solution for Infusion	medinfo@peckforton.com; summerfield@riemser.com annalisa@cherubino.com.mt	+44 (0)1628771800 +356 21343270
Clonmel Healthcare Limited	Profloxin Tablet, film-coated 250mg Profloxin Tablet, film-coated 500mg	medicalinformation@clonmel-health.ie	+353526177777
COOPER S.A. Pharmaceuticals	Nafloxin Injectable Solution for Infusion 200mg/100ml LEVOFLOXACIN/COOPER 500mg/100ml solution for I.V. infusion	akourvetaris@zeincro.com	+30 210 8047709
Delorbis Pharmaceuticals Limited	Viprolox 250mg Film coated tablets Viprolox 500mg Film-coated tablets Floxaval 500mg Film-coated tablets	delorbis@delorbispharma.eu	+357 22 845 000
DEMO S.A. Pharmaceutical Industry	Levofloxacin Solution for Infusion 5mg per ml	pv@demo.gr	+30 2108161802
Fresenius Kabi Italia S.r.l	Ciprofloxacin Kabi 200mg/100ml solution for infusion	paola.ragazzo@fresenius-kabi.com	+390456649402
Fresenius Kabi Limited	Levofloxacin 5mg/ml solution for infusion	paola.ragazzo@fresenius-kabi.com	+390456649402
Ibigen S.r.L	Levofloxacin Ibigen 5mg/ml solution for infusion Ciprofloxacin Ibigen 100mg/50ml solution for infusion Ciprofloxacin Ibigen 200mg/100ml solution for	abusuttill@drugsalesltd.com	+356 21419070/1/2

Company	Product name	Email	Phone
	infusion Ciprofloxacin Ibigen 400mg/200ml solution for infusion		
KRKA, d. d., Novo Mesto	Ciprinol 250mg film-coated Tablets Ciprinol 500mg film-coated Tablets	pharmacovigilance@krka.biz	+386 1 47 51 100
Medochemie Limited	Medociprin AMESOL 500mg Film- Coated Tablets	alex.fenech@europharma.com.mt	+356 2385 9239
Mylan S.A.S.	Levofloxacin Mylan Solution for Infusion 500mg/100ml Levofloxacin Mylan Solution for Infusion 250mg/50ml	info.uk@mylan.co.uk	+356 22983143
Noridem Enterprises Ltd	Ciprofloxacin Solution for Infusion 2mg/ml	pv@demo.gr	+30 2108161802
Norma Hellas S.A.	Revionorm Solution for Infusion 200mg/100ml	safety@pharmassist.gr merkouri@pharmassist.gr	+30 210 65 61 435
P & D Pharmaceutical s Limited	Ciprofloxacin 2mg/ml, Solution for Infusion Levofloxacin Solution for Infusion 5mg/ml	info@pdpharm.co.uk	01420487501
PIAM Farmaceutici S.p.A.	TRISSIL 500mg film-coated tablets	piam@gbpharmaservices.it	+39 3461524287
Remedica Limited	Zindolin 250 Tablets Zindolin 500 Coated Tablets	A.Vasiliou@remedica.com.cy	+357 25553251
Rowex Ltd	Cifox Tablet, film coated 250mg Cifox Tablet, film coated 500mg Cifox Tablet, film coated 750mg	pv@rowa-pharma.ie	+3532750077
S.C. AC Helcor Pharma S.R.L.	Ciprolen Tablet, film coated 250mg Ciprolen Tablet, film coated	admin@achelcor.ro	+400362401206

Company	Product name	Email	Phone
	500mg		
Sanofi Malta Limited	Tavanic 500mg film-coated tablet	Graziella.Gravino@sanofi.com	+356 21493022
TAD Pharma GmbH	Norflosal	Drug-Safety@tad.de	+ 49 (0) 4721 606 0
Villerton Invest S.A.	Ciprofloxacin 2mg/ml solution for infusion	abusuttil@drugsalesltd.com	+356 21 419 070/1/2

Yours faithfully,

**Post-Licensing Directorate
Medicines Authority**

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf Accord Healthcare Limited, Actavis Group PTC ehf, Anfarm Hellas S.A., Bayer PLC, Beximco Pharma UK Ltd, Bial - Portela & C S.A., Chiesi Farmaceutici S.p.A., Claris Lifesciences UK Limited, Clonmel Healthcare Limited, COOPER S.A. Pharmaceuticals, Delorbis Pharmaceuticals Limited, DEMO S.A. Pharmaceutical Industry, Fresenius Kabi Italia S.r.l., Fresenius Kabi Limited, Ibigen S.r.L, KRKA, d. d., Novo Mesto, Medochemie Limited, Mylan S.A.S., Noridem Enterprises Ltd, Norma Hellas S.A., P & D Pharmaceuticals Limited, PIAM Farmaceutici S.p.A., Remedica Limited, Rowex Ltd, S.C. AC Helcor Pharma S.R.L., Sanofi Malta Limited, TAD Pharma GmbH, Villerton Invest S.A.