KRKA Pharma Dublin Ltd.

Direct Healthcare Professional Communication

29th October 2020

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

Dear Healthcare professional,

Marketing Authorisation Holders of fluoroquinolone antibiotics products (see Table 1), in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) 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 circulation in March/April 2019, www.hpra.ie). 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 circulation in October 2018, www.hpra.ie).

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.

Call for reporting

Reporting suspected adverse reactions after authorisation of medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

Company contact point

Suspected adverse reaction reports should also be reported to the relevant Marketing Authorisation Holders (Table 1 below). For additional information, please contact the relevant Marketing Authorisation Holders below.

Table 1

Marketing Authorisation Holder	**Product Name**	**Email**	**Phone**
Accord Healthcare Ireland Ltd.	Ciplox (ciprofloxacin) 250 mg Film-coated Tablets Ciplox (ciprofloxacin) 500 mg Film-coated Tablets Ciplox (ciprofloxacin) 750 mg Film-coated Tablets	medinfo@accord-healthcare.com / Online form at www.accord-healthcare.ie/drug-reaction-report	+44 (0) 1271 385 257
A. Menarini Industrie Farmaceutiche Riunite – s.r.l.	Quofenix (delafloxacin) 450 milligram(s) Tablets Quofenix (delafloxacin) 300 milligram(s) Pdr/Conc/Soln for infusion	medinfo@menarini.ie	+353 1 284 6744
Bayer Ltd.	Ciproxin (ciprofloxacin) 250 mg Film-coated Tablets Ciproxin (ciprofloxacin) 500 mg Film-coated Tablets Ciproxin (ciprofloxacin) 750 mg Film-coated Tablets Ciproxin (ciprofloxacin) Solution for infusion 2 mg/ml Avelox (moxifloxacin) 400 mg Film-coated Tablets Avelox (moxifloxacin) 400 mg/250 ml Solution for infusion	medinfo.ireland@bayer.com	+353 1 216 3300
Bluefish Pharmaceuticals AB	Levofloxacin Bluefish 250 mg Film-coated Tablets Levofloxacin Bluefish 500 mg Film-coated Tablets	drugreaction@bluefishpharma.com	+46 8 51911600
Chiesi Ltd.	Quinsair (levofloxacin) 240 mg Nebuliser solution	pv.uk@chiesi.com	+44 (0)161 488 5555
Clonmel Healthcare Ltd.	Profloxin (ciprofloxacin) 250 mg Film-coated Tablets Profloxin (ciprofloxacin) 500 mg Film-coated Tablets	medicalinformation@clonmel-health.ie	+353 52 617 7777
Fannin Ltd.	Truoxin (ciprofloxacin) 250 mg Film-coated Tablets Truoxin (ciprofloxacin) 500 mg Film-coated Tablets	medical@dccvital.com	+353 (0)1 2907000
Fresenius Kabi Deutschland GmbH	Levofloxacin 5mg/ml Solution for infusion Moxifloxacin 400 mg/250 ml Solution for infusion	Pharmacovigilance.GB@fresenius-kabi.com	+44 (0)1928 533 612

Marketing Authorisation Holder	Product Name	Email	Phone
Hikma Farmacêutica (Portugal), S.A	Truoxin (ciprofloxacin) I.V. 200mg/100ml Solution for infusion Truoxin (ciprofloxacin) I.V. 400mg/100ml Solution for infusion Levofloxacin 5mg/ml Solution for infusion	portugaleupharmacovigilance@hikma.com	+351 210 438 540
Krka d.d. Novo mesto	Ciprofloxacin Krka 250 mg Film-coated Tablets Ciprofloxacin Krka 500 mg Film-coated Tablets Ciprofloxacin Krka 750 mg Film-coated Tablets Levofloxacin Krka 250 mg Film-coated Tablets Levofloxacin Krka 500 mg Film-coated Tablets	pharmacovigilance.ie@krka.biz	+353 1 293 9180
McDermott Laboratories Ltd. (Mylan)	Cifloxager (ciprofloxacin) 250 mg Film-coated Tablets Cifloxager (ciprofloxacin) 500 mg Film-coated Tablets Tavager (levofloxacin) 500 mg Film-coated Tablets	info.uk@mylan.co.uk ukpharmacovigilance@mylan.com	+44 1707 853 0000
Noridem Enterprises Ltd.	Ciprofloxacin 2 mg/ml Solution for infusion Levofloxacin 5mg/ml Solution for infusion	pv@demo.gr	+30 210 8161802
Pfizer Healthcare Ireland	Ciprofloxacin 2 mg/ml Solution for infusion	RegAffairsInfo@pfizer.com	+353 1 467 6546
Rowex Ltd.	Cifox (ciprofloxacin) 250 mg Film-coated Tablets Cifox (ciprofloxacin) 500 mg Film-coated Tablets Cifox (ciprofloxacin) 750 mg Film-coated Tablets	pv@rowa-pharma.ie	+35327 50077
Sanofi-Aventis Ireland Ltd. T/A SANOFI	Tavanic (levofloxacin) 5 mg/ml Solution for infusion Tavanic (levofloxacin) 250 mg Film-coated Tablets Tavanic (levofloxacin) 500 mg Film-coated Tablets Tarivid (ofloxacin) 200 mg Film-Coated Tablets	IEmedinfo@sanofi.com	+353 1 403 5600
Teva Pharma B.V.	Ciprofloxacin Teva 250 mg Film-coated Tablets Ciprofloxacin Teva 500 mg Film-coated Tablets	medinfo@tevauk.com	+44 (0)20 7540 7117

Yours faithfully

Feroze Nazneen
Lead Representative and Local Responsible Person for Pharmacovigilance
Regulatory Manager and Authorised Person for Quality System Management
Krka Pharma Dublin Ltd.
Signed on behalf of the Marketing Authorisation Holders listed in Table 1 above

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.*