Direct Healthcare Professional Communication

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

Dear Healthcare professional,

Marketing authorisation holders of fluoroquinolone antibiotics products in agreement with the European Medicines Agency and the <National Competent 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 circulation in March/April 2019, link to national website if applicable). 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, link to national website if applicable).

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 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 the national reporting system [include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system].

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

TO BE COMPLETED LOCALLY

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.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	NAPs: Ciprofloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Norfloxacin; Ofloxacin; Pefloxacin; Prulifloxacin; Rufloxacin. CAPs: Delafloxacin (Quofenix), Levofloxacin (Quinsair). For systemic and inhalation route.
Marketing authorisation holder(s)	Various. In cases where the DHPC concerns several marketing authorisation holders of the same active substance or is part of a class review, it is strongly encouraged that a single consistent message is sent to healthcare professionals in each EU Member State. All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State. It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.
Safety concern and purpose of the communication	Addition of a new warning regarding a possible risk of heart valve regurgitation/incompetence associated with fluoroquinolone systemic and inhalation use.
DHPC recipients	General practitioners, prescribing specialists (ENT, pulmonologists, urologists, infectiologists) and diagnosing specialists (cardiologists, radiologists, and emergency units) and relevant learned societies. If needed, further recipients may be discussed at national level.
Member States where the DHPC will be distributed	All EU member States where fluoroquinolones are marketed.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	3 Sept 2020
DHPC and communication plan (in English) agreed by CHMP	17 Sept 2020
Submission of translated DHPCs to the national competent authorities for review	8 Oct 2020
Agreement of translations by national competent authorities	15 Oct 2020
Dissemination of DHPC	29 Oct 2020