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Fluoroquinolones: risk of cardiac valve insufficiency

Quick Read
Due to a risk of mitral and aortic regurgitation in patients with risk factors, fluoroquinolones in systemic and inhalation formulations should only be used after careful consideration of the benefit-risk balance and of alternative therapeutic options.

Fluoroquinolones are broad-spectrum antibiotics approved in the European Union for the treatment of certain types of bacterial infections, some of which are potentially lethal.

Factors increasing the risk of cardiac valve regurgitation/insufficiency include pre-existing or congenital cardiac valvulopathy, connective tissue conditions (e.g., Marfan syndrome, Ehlers-Danlos syndrome), hypertension, Turner's syndrome, Behçet's disease, rheumatoid arthritis, infective endocarditis.

Since they can cause serious and long-term adverse reactions, the use of fluoroquinolones is **restricted** to infections in which other recommended first-line antibiotics are not considered adequate.

In 2018, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) looked at a safety signal regarding **aortic aneurysm and aortic dissection** associated with fluoroquinolone use. Data from epidemiological and non-clinical studies pointed to a two-fold higher risk of aortic aneurysm and aortic dissection in patients on systemic fluoroquinolones when compared with other patients who had received no antibiotics or who had taken other other antimicrobials (amoxicillin). The risk was higher in the elderly.

In 2019, following the publication of a an epidemiological study by **Etminan *et al*** that showed that patients who had received systemic fluoroquinolones had a risk of mitral and aortic regurgitation that was twice as high as that of patients on other antibiotics (amoxicillin or azithromycin), the PRAC started a safety signal assessment on cardiac valve regurgitation/insufficiency.

Cont'd ▶

The Portuguese National Pharmacovigilance System is counting on healthcare professionals to keep reporting any ADRs that may occur with medicinal products used in the treatment of COVID-19 – see infografic (in Portuguese)

Fluoroquinolones:
risk of cardiac valve insufficiency

▶ *Cont'd*

Several reports were received of clinically confirmed cases of cardiac valve (any valve) regurgitation/insufficiency in patients on fluoroquinolones, with a possible or a probable causality nexus. In addition, an experimental study (**Guzzardi DG *et al***) showed that exposure to ciprofloxacin led to degradation of collagen in aortic myofibroblasts donated by patients with aortic pathology including regurgitation. Collagen matrix degradation has also been linked to other aorta and tendon conditions associated with the use of fluoroquinolones.

With all the available evidence, the PRAC concluded in September 2020 that, in patients at risk of cardiac valve regurgitation/insufficiency, fluoroquinolones (systemic or inhalation routes) should only be used after careful consideration of the benefit-risk balance and of other therapeutic options. Changes to the **Summaries of the Product's Characteristics and Patient Information Leaflets** were recommended, as well as a Communication to healthcare professionals.

Patients should be advised to seek immediate medical assistance should they develop acute dyspnoea, de novo palpitations or abdominal or lower extremity oedema.

Magda Pedro

Communications to Healthcare Professionals published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Fluoroquinolones Systemic (per os and injection) and inhalation	**Physicians:** general/family medicine, ENT, pneumology, urology, nephrology, infectious diseases, internal medicine, tropical medicine, cardiology, and radio-diagnosis; heads of emergency dpts	Risk of cardiac valve regurgitation/insuficiency 29-10-2020
Pirfenidone Esbriet	**Physicians:** pneumology, internal medicine and gastroenterology **Pharmacists:** hospital	Prevention of drug-induced injury 29-10-2020

Compiled by Patrícia Catalão

INDEX CARD

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Cyproterone acetate: risk of meningioma

Quick Read
Cyproterone acetate can be associated with the occurrence of meningioma, especially when used in higher doses and for prolonged periods of time.

Cyproterone acetate is a synthetic progestogen with anti-androgenic properties. Therapeutic indications for monotherapy in women (10 mg and 50 mg doses) include signs and symptoms of androgenization, such as moderately severe hirsutism, moderately severe or severe androgenetic alopecia, as well as severe and moderately severe forms of acne and seborrheic dermatitis. In men (50 mg, 100 mg, and 300 mg/3ml doses), they include anti-androgenic treatment in inoperable prostate carcinoma and reduction of sex drive in cases of sexual deviation.
Meningiomata are the most common intracranial neoplasms and they are mostly considered to be benign. Their symptoms are non-specific and location dependent.

An association between meningiomas and cyproterone acetate in daily doses of 50 mg had already been described in 2008 (**Froelich S *et al***). However, a French pharmacoepidemiological study published in 2019 (**Weill *et al***) prompted a risk assessment by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC).

Analysis of this study's data, as well as post-marketing data and data from other articles in the literature, has shown that most cases of meningioma reported in association with the use of cyproterone acetate occurred when this drug was **given for over 5 years in daily doses of 50 mg or more**. On the other hand, at least four cases were sufficiently well documented to allow for a causal link to be established between the development of meningiomas and short-term use of high doses of cyproterone acetate.

The **PRAC** thus **concluded** that the above data should be reflected in the Summaries of the Product's Characteristics (SmPCs) and Patient Information Leaflets (PLs). **Recommendations**:

- Products containing doses of cyproterone higher than 10 mg should only be prescribed in androgen-dependent conditions, such as hirsutism, androgenetic alopecia, acne and seborrheic dermatitis, whenever satisfactory results could not be obtained with low doses of cyproterone or with other therapeutic options. Once clinical improvement is obtained, the dose should be gradually reduced to the lowest effective dose.
- Products containing cyproterone should only be used to reduce sex drive whenever other treatment options are not adequate.
- The use of these medicinal products for inoperable prostate cancer remains unchanged.
- Symptoms suggesting meningioma should be watched out for, in line with clinical practice.
- In case of a diagnosis of meningioma, cyproterone acetate should be definitively discontinued.

No new safety issue has been identified concerning a risk of meningioma in association with the use of medicinal products containing **low doses of cyproterone acetate / ethynilestradiol and cyproterone acetate / estradiol valerate**. Nevertheless, since the risk of meningioma increases with increasing cumulative doses of cyproterone, those products are now **contraindicated in patients with meningioma** or with a **past history** of meningioma.

Márcia Silva

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Alpelisib Piqray	**Physicians:** oncologists	Healthcare professional guide 15-10-2020
Ambrisentan Ambrisentano Mylan	**Patients**	Memory card 07-10-2020
Brolucizumab Beovu	**Patients**	Guide 07-10-2020
Daratumumab Darzalex	**Physicians:** haematology dpt directors, haematologists, immune-haemotherapy dpt directors **Pharmacists:** hospital	Guide for healthcare professionals 07-10-2020
	Healthcare professionals: blood banks	Guide for blood bank professionals
	Patients	Patient card 22-10-2020
Delamanid Deltyba	**Healthcare professionals:** in charge of prescription, dispensing and administration	Guide for healthcare professionals
	Patients	Patient guide 09-10-2020
Etanercept Benepali	**Physicians:** rheumatologists and dermatologists	Additional risk minimization measures 03-10-2020
Pirfenidone Esbriet	**Physicians:** pneumologists	Safety checklist 29-10-2020
Ranibizumab Lucentis	**Patients**	Guide for the treatment of loss of vision due to diabetic macular oedema (DMO) and progressive diabetic retinopathy 13-10-2020
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	Patients	Patient education leaflet Alert card 24-10-2020
Tolvaptan Jinarc	**Médicos:** nephrologists	Guide for use
	Patients	Patient education brochure Alert card 29-10-2020

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