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(IN REPLY PLEASE QUOTE THIS FILE REF.)

23 Jan 2024

Dear Healthcare Professionals,

Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate in the United Kingdom

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that systemic fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate. This follows a review by the MHRA which looked at the effectiveness of current measures to reduce the identified risk of disabling and potentially long-lasting or irreversible side effects.

Systemic and inhaled fluoroquinolones are associated with a risk of serious, disabling, long-lasting and potentially irreversible adverse reactions, estimated to occur in at least between 1 and 10 people in every 10,000 who take a fluoroquinolone. These may affect multiple body systems and include musculoskeletal, nervous, psychiatric and sensory reactions. These adverse reactions have been reported in patients irrespective of their age and potential risk factors.

Patients have reported that experiencing long-lasting or disabling reactions can affect their mental health, particularly when they perceive healthcare professionals fail to adequately acknowledge the reactions or the possibility that they are associated with a fluoroquinolone. Tendon damage can occur within 48 hours of commencing treatment, or the effects can be delayed for several months and become apparent after stopping treatment.

There are no proven drug treatments for these side effects. However, it is important that fluoroquinolones are stopped immediately at the first signs of a musculoskeletal, neurological or psychiatric side effect to avoid further exposure, which could potentially worsen adverse reactions. These symptoms should be appropriately investigated.

Restrictions to the use of fluoroquinolones were introduced in 2019 to minimise the risk of these reactions. The MHRA has reviewed the effectiveness of these measures in the United Kingdom and sought the advice of the Commission on Human Medicines. As a result of this review a reminder about these risks was published in Aug 2023.

The MHRA has now taken additional regulatory action to update the indications for all systemic fluoroquinolones to state they should only be used when other commonly recommended antibiotics are inappropriate. Situations where other antibiotics are considered to be inappropriate are where:

- There is resistance to other first-line antibiotics recommended for the infection.
- Other first-line antibiotics are contraindicated in an individual patient.
- Other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped.
- Treatment with other first-line antibiotics has failed.

The description of disabling and potentially long-lasting or irreversible side effects in the safety information has also been updated, to include more detail about the range of psychiatric symptoms that may occur as part of these reactions. These may include sleep disorders, anxiety, panic attacks, confusion or depression. While the frequency of disabling and potentially long-lasting or irreversible side effects cannot be estimated precisely using available data, the updated reporting incidence indicates a minimum frequency of between 1 and 10 per 10,000 patients.

Advice for healthcare professionals:

- Systemic (by mouth, injection, or inhalation) fluoroquinolones can cause long-lasting (up to months or years), disabling and potentially irreversible side effects, sometimes affecting multiple body systems and senses.
- The United Kingdom indications for systemic fluoroquinolones have been updated so they must only be used in situations when other antibiotics, that are commonly recommended for the infection, are inappropriate.
- Situations in which other antibiotics are considered to be inappropriate and where a fluoroquinolone may be indicated are where: there is resistance to other first-line antibiotics recommended for the infection; other first-line antibiotics are contraindicated in an individual patient; other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped; treatment with other first-line antibiotics has failed.
- This goes further than previous measures which set out that fluoroquinolones should not be prescribed for non-severe or self-limiting infections, or non-bacterial conditions, for example, non-bacterial (chronic) prostatitis. These measures are still in place.
- As a reminder, patients should be advised to stop fluoroquinolone treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and central nervous system effects, and to contact their doctor immediately.

- Remain alert to the risk of suicidal thoughts and behaviours with use of fluoroquinolone antibiotics. A reminder about these risks was published in Sep 2023.
- As a reminder of advice published in Aug 2023: avoid fluoroquinolone use in patients who have previously had serious adverse reactions with a quinolone antibiotic (for example, nalidixic acid) or a fluoroquinolone antibiotic; prescribe fluoroquinolones with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury; avoid coadministration of a corticosteroid with a fluoroquinolone since this could exacerbate fluoroquinolone-induced tendinitis and tendon rupture.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-must-now-only-be-prescribed-when-other-commonly-recommended-antibiotics-are-inappropriate

In Hong Kong, there are registered pharmaceutical products containing systemic fluoroquinolones for use in human, including ciprofloxacin (51 products), levofloxacin (44 products), moxifloxacin (6 products), norfloxacin (3 products), ofloxacin (14 products) and prulifloxacin (one product). All products are prescription-only medicines.

So far, the Department of Health (DH) has received adverse drug reaction with regard to levofloxacin (13 cases; of which 3 cases were reported as musculoskeletal, nervous and/or psychiatric reactions) and ofloxacin (4 cases; all of these cases were reported as attempted suicide/completed suicide). The DH has received adverse drug reaction related to ciprofloxacin (one case) and moxifloxacin (one case), but these cases were not related to the disabling side effects mentioned in the above MHRA's announcement. The DH has not received any case of adverse drug reaction related to norfloxacin and prulifloxacin.

Related news on the risk of musculoskeletal, nervous and psychiatric adverse reactions associated with the use of fluoroquinolones was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 8 Nov 2011, with the latest update posted on 27 Sep 2023. Letters to inform local healthcare professionals were issued by the DH on 8 Nov 2011, 16 Aug 2013, 13 May 2016, 11 Jul 2018 and 8 Oct 2018.

In Jun 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack labels and/or package inserts of locally registered pharmaceutical products containing fluoroquinolones for systemic use should contain safety information about the risk of disabling and potentially irreversible serious adverse reactions (including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects).

In light of the above MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Clinical Trials and Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Terence MAN)
for Assistant Director (Drug)