Direct Healthcare Professional Communication

April 2022

Increased risk of Cardiovascular Events & Cardiovascular Mortality when Hydroxychloroquine or Chloroquine used with Macrolide antibiotics

Dear Healthcare Professional,

The Egyptian Pharmaceutical Vigilance Center of the Central Administration for Pharmaceutical Care at The Egyptian Drug Authority would like to inform you of the following:

Summary

- An observational study in patients with rheumatoid arthritis has shown that co-administration of azithromycin with hydroxychloroquine is associated with an increased risk of cardiovascular events and cardiovascular mortality.
- Carefully consider the benefits and risks before prescribing systemic Azithromycin or other systemic Macrolide antibiotics (Erythromycin or Clarithromycin) to patients being treated with Hydroxychloroquine or Chloroquine.

Further information on the safety concern and the recommendations

- If there is a clinical need to prescribe systemic macrolide antibiotics with hydroxychloroquine or chloroquine, use caution in patients with risk factors for cardiac events and follow advice in the product information for each medicine.
- Be vigilant for psychiatric reactions associated with hydroxychloroquine or chloroquine, especially in the first month of treatment; events have been reported in patients with no prior history of psychiatric disorders.
- Healthcare professionals shall advice patients and carers with:
    - Some antibiotics (known as macrolides) taken by mouth or given as an injection at the same time with hydroxychloroquine or chloroquine have been associated with an increased risk of side effects that affect the heart.
    - Seek urgent medical help if you have any signs of problems with your heart (for example, palpitations, fainting, chest pain, or unexplained breathlessness).
    - Some patients have also reported mental health symptoms when they started treatment with hydroxychloroquine or chloroquine.
    - Speak to your doctor as soon as possible if you or your family members or caregivers notice any new or worsening mental health symptoms.

Hydroxychloroquine and chloroquine indications

Hydroxychloroquine is indicated for treatment of rheumatoid arthritis, systemic lupus erythematosus, and dermatological conditions aggravated by sunlight. Chloroquine is indicated for malaria prophylaxis or

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treatment, with some products also having indications for treatment of amoebic hepatitis and abscess, rheumatoid arthritis, and discoid or systemic lupus erythematosus.

Review of cardiovascular safety after observational trial

- An observational retrospective study published in August 2020 compared records of adverse events in patients initiated on hydroxychloroquine alone with those in patients initiated on sulfasalazine alone for rheumatoid arthritis. The same study compared severe adverse events associated with use of hydroxychloroquine plus azithromycin with those associated with use of hydroxychloroquine plus amoxicillin.
- The study showed that in a short-term period (up to 30 days) after first use of hydroxychloroquine treatment in combination with azithromycin there was an increased risk of angina or chest pain, heart failure, and cardiovascular mortality compared with the combination of hydroxychloroquine and amoxicillin.
- No excess risk of severe adverse events was identified in the short-term period of hydroxychloroquine alone (compared with sulfasalazine), but longer-term use past 30 days was associated with increased cardiovascular mortality.
- Although the mechanism of the observed effects was not examined in detail by the study, it has been proposed that events could be caused by cumulative effects of hydroxychloroquine and azithromycin on the QT interval, potentiating arrhythmias and cardiac death, or through other additive cardiotoxic effects more generally.
- A national review of safety data by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines considered these data. We have published a Public Assessment Report of this assessment.
- The review recommended that the product information for hydroxychloroquine and systemic azithromycin medicines should be amended to include new warnings and advice on these risks. Due to the similar safety profiles, the risks seen with concurrent use of hydroxychloroquine and azithromycin are considered to apply to concurrent use of hydroxychloroquine and other systemic macrolide antibiotics (clarithromycin or erythromycin) and to use of chloroquine with systemic macrolide antibiotics. As such, the review recommended that similar warnings should also be added to the product information for chloroquine and for systemic clarithromycin or erythromycin.
- These warnings are not being introduced for topical macrolide products (which are indicated for conjunctivitis or acne), as these products are used at lower doses and with very limited potential for systemic exposure, and do not list cardiovascular events as potential adverse effects associated with their use.

References

MHRA

https://www.gov.uk/drug-safety-update/hydroxychloroquine-chloroquine-increased-risk-of-cardiovascular-events-when-used-with-macrolide-antibiotics-reminder-of-psychiatric-reactions

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Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions via the Egyptian reporting system:

Name: Egyptian Pharmaceutical Vigilance Center

Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451 Telephone: +202- 25354100, Extension: 1470 Fax: +202 – 23610497

Email: pv.followup@edaegypt.gov.eg

Online reporting: https://primaryreporting.who-umc.org/EG
QR Code:

Hotline: 15301

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