SAFETY ALERT

DRAP SAFTEY ALERT NO. 28

Increased Risk of Cardiovascular Events with Co-administration and Interaction Between Hydroxychloroquine or Chloroquine, and Macrolide Antibiotics

Date: 29th of November, 2022.

Target Audience:

- Manufacturers and importers of hydroxychloroquine or chloroquine, and systemic macrolide antibiotics;
- Healthcare professionals; and
- Patients, consumers or caregivers.

Background:

The MHRA on 15th February, 2022 announced that the product information for hydroxychloroquine, chloroquine and macrolide antibiotics (azithromycin, erythromycin or clarithromycin) will be revised to include the increased risk of cardiovascular events and cardiovascular mortality if hydroxychloroquine or chloroquine is taken with a macrolide-antibiotic. A review was conducted by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines following the results of a retrospective observational study which shows that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events (including angina or chest pain and heart failure) and cardiovascular mortality.

It was recommended in the review that the product information for hydroxychloroquine and systemic azithromycin medicines should be amended to include new warnings and advice on these risks. Owing to the similar safety profiles, the risks with concurrent use of

hydroxychloroquine and azithromycin were considered to apply to the concurrent use of hydroxychloroquine and other systemic macrolide antibiotics (clarithromycin or erythromycin) and to the use of chloroquine with systemic macrolide antibiotics. Therefore, the review recommended that similar warnings should also be added to the product information for chloroquine and for systemic clarithromycin or erythromycin. However, these warnings were not being introduced for topical macrolide products (which are indicated for conjunctivitis or acne).

The MHRA also reminded the healthcare professionals that the product information for hydroxychloroquine and chloroquine already contains warnings about cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcomes. It was also informed that evidence suggests both hydroxychloroquine and chloroquine can prolong the QT interval, especially in overdose or when used in combination with other medicines with the potential to induce cardiac arrhythmias. Likewise, warnings are also in place across the product information for azithromycin, clarithromycin, and erythromycin to use caution in patients with a history of QT interval prolongation or in patients receiving a medicine known to cause QT prolongation. Although the mechanism of the observed effects was not examined in detail by the study, it was proposed that events could have been 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.

Action in Pakistan:

Accordingly, the case of risk of cardiovascular events with co-administration and interaction between hydroxychloroquine or chloroquine, and macrolide antibiotics was discussed in the 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP). The PRAEC-DRAP after discussion decided as per Rule 10 (1) (h) (iv) and (vi)

of Pharmacovigilance Rules, 2022 (reliance mechanism) to update prescribing information (warning and interaction sections) of hydroxychloroquine, chloroquine and macrolide antibiotics

(azithromycin, erythromycin or clarithromycin excluding topical macrolides) about the potential interaction of increased risk of cardiovascular events and cardiovascular mortality if hydroxychloroquine or chloroquine is taken with a macrolide-antibiotic

Therapeutic Goods Affected:

Name: **Hydroxychloroquine**
Chloroquine; and
Systemic macrolide antibiotics (not topical).

Hydroxychloroquine is indicated for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and dermatological conditions aggravated by sunlight. Chloroquine is indicated for malaria prophylaxis or treatment and other indications. Macrolide antibiotics such as erythromycin, clarithromycin and azithromycin are used to manage and treat various bacterial infections like pneumonia, sinusitis, pharyngitis and tonsillitis etc.

Advice for patients:

Patients are informed that some antibiotics (known as macrolides) taken by mouth or given as an injection at the same as 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, palpitation, fainting, chest pain, or unexplained breathlessness).

Advice for healthcare professionals:

Healthcare professionals are informed that an observational study has shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events (including angina or chest pain and heart failure) and cardiovascular mortality. Therefore, 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. 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.

Guidelines for reporting of Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with hydroxychloroquine or chloroquine, and macrolide antibiotics to the National Pharmacovigilance Centre**,** Drug Regulatory Authority of Pakistan through Med Vigilance E-Reporting system available on the DRAP website.

Similarly, ADRs can also be reported through Med Safety App which is available for download from App store (for iOS devices) and Google Play (for Android devices).

References:

1. Minutes of 1st meeting of Pharmacovigilance Risk Assessment Expert Committee of the DRAP.
2. MHRA update regarding Hydroxychloroquine, chloroquine: increased risk of cardiovascular events when used with macrolide antibiotics; reminder of psychiatric reactions.