Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Hydroxychloroquine or chloroquine, in combination with macrolide antibiotics: review of epidemiological data for cardiovascular safety

MHRA Public Assessment Report
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Contents

1. Plain language summary

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines (CHM) have reviewed the available safety data for the use of hydroxychloroquine (a medicine used to treat conditions such as rheumatoid arthritis) at the same time as an antibiotic called azithromycin from the group known as macrolides.

This review was triggered by evidence from a study published in August 2020. This study focused on people who took hydroxychloroquine for rheumatoid arthritis at the same time as azithromycin and compared outcomes with people who took hydroxychloroquine at the same time as different type of antibiotic called amoxicillin.

The study showed that people who take hydroxychloroquine at the same time as azithromycin were more likely to get side effects affecting the heart compared with people who take hydroxychloroquine at the same time as amoxicillin. These side effects include chest pain or the heart being unable to pump blood around the body properly (heart failure).

These events were identified within a short period of time (up to 30 days) after starting to take these medicines together.

Based on this evidence, information about these risks has been added to the product information for hydroxychloroquine and the related medicine chloroquine. Warnings have also been added to the product information for azithromycin and two other macrolide antibiotics called clarithromycin and erythromycin. A Drug Safety Update has been published to communicate these risks to healthcare professionals.

About hydroxychloroquine and chloroquine

Hydroxychloroquine is used in adults to treat some conditions caused by the body's natural defence system (immune system) wrongly attacking parts of the body. These immune conditions include rheumatoid arthritis, certain types of lupus erythematosus, and some skin conditions that are caused by sunlight or made worse by sunlight.

In children, hydroxychloroquine is used to treat certain types of lupus erythematosus, and is also used at the same time as other medicines to treat some types of childhood arthritis (juvenile idiopathic arthritis).

Chloroquine is used to prevent and to treat malaria in adults and children. It is also used in adults only to treat inflammation and build-up of pus in the liver caused by microscopic parasites (amoebic hepatitis and abscess), as well as to treat rheumatoid arthritis and types of lupus erythematosus.

About macrolide antibiotics

The macrolide drug group are antibiotics used to treat acute and chronic infections. These medicines are effective treatments for a range of infections. The penicillin group of antibiotics (including amoxicillin) are used to treat a similar range of infections. This means that macrolides are often used as an alternative in patients who are allergic to penicillin.

The three main macrolide antibiotics used in the UK are azithromycin, clarithromycin and erythromycin:

- Azithromycin is used in infections of the respiratory tract; ear, skin and soft tissue infections; infections of the urethra; and sexually transmitted infections including chlamydia and gonorrhoea.
- Clarithromycin is used to treat infections including in the respiratory tract; ear, mouth, skin and soft tissue; and also treating stomach ulcers caused by the bacteria *Helicobacter pylori*.
- Erythromycin is used in infections of the respiratory tract, ear, eyes or mouth; skin and soft tissue infections; infections of the stomach and intestines; infections of the urethra; and sexually transmitted infections including syphilis, chlamydia and gonorrhoea.

Reason for the review and how it was done

In August 2020, a study by Lane and colleagues was published that looked at the safety of hydroxychloroquine in patients taking this medicine for rheumatoid arthritis. The study used data from healthcare databases from several different countries, including the UK. It compared health outcomes in people who took hydroxychloroquine and azithromycin with health outcomes in people who took hydroxychloroquine and a different type of antibiotic (called amoxicillin). It also compared health outcomes in people who took hydroxychloroquine with health outcomes in people who took a different medicine for rheumatoid arthritis called sulfasalazine.

The MHRA reviewed the data from the study from Lane and colleagues together with other evidence up to November 2020 from the published scientific literature and from databases of suspected medicines side effect reports. The review aimed to determine if any action was needed to minimise the risks to patients using these medicines.

The MHRA received independent advice on this review from the Pharmacovigilance Expert Advisory Group, an independent group of experts that advises the Commission on Human Medicines on the safety of medicines.

Conclusions of the review

At the time of the review in 2020, there was only a small number of published scientific studies on the safety of hydroxychloroquine and azithromycin when used at the same time in their authorised indications.[1]

The greatest amount of evidence on the safety of this combination in a post-marketing setting comes from the large study by Lane and colleagues. This is currently the most useful evidence as it provides a comparison of safety outcomes in these patients compared with other patients taking medicines with similar indications.

The study by Lane and colleagues showed that people who take hydroxychloroquine at the same time as azithromycin are more likely to get side effects affecting the heart within a short period of time (up to 30 days) of starting to take these medicines together, compared with people who take hydroxychloroquine at the same time as amoxicillin.

Hydroxychloroquine is an effective treatment for lifelong conditions such as rheumatoid arthritis, which can have a significant impact on people's health and quality of life if they are not adequately treated. Azithromycin is used to treat infections, including some that can be serious or life-threatening.

There may be some situations in which the benefit of being able to treat a serious infection with azithromycin in a patient who is also taking hydroxychloroquine is greater than the risks to that patient of side effects affecting the heart. For example, if other antibiotics are not effective in treating a serious infection. However, it is important for healthcare professionals and patients to be aware of these risks, and for healthcare professionals to carefully consider the benefits and the risks before prescribing these medicines at the same time.

Information about these risks has now been added to the product information for healthcare professionals and patients for hydroxychloroquine and azithromycin. Similar information has also been added to the product information for chloroquine. This is because it is a medicine very similar to hydroxychloroquine and may cause similar types of side effects. Similar information has also been added to the product information for the antibiotics clarithromycin and erythromycin. This is because they are part of the same group of antibiotics as azithromycin (macrolide antibiotics) and may cause similar types of side effects.

The product information updates for macrolide antibiotics are only for medicines that affect the whole body, such as tablets that are swallowed or dissolved in water and solutions that are injected. The same risks do not apply to products intended for application to the skin or for use as eye drops.

These changes to the product information have also been communicated to UK healthcare professionals in a Drug Safety Update article.

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[1] This remains the case at time of publication in February 2022, and no newer studies have been identified that alter the conclusions of this MHRA review.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines (CHM) advises government ministers and the MHRA on the safety, efficacy and quality of medicines, taking into account the advice from its various Expert Advisory Groups.

The aim of our Safety Public Assessment Reports is to present evidence-based assessments of safety issues for a particular drug or drug class.

A glossary is provided for an explanation of the terms used in this report (see section 9)

This report provides a summary of the review of available safety data on the cardiovascular safety of hydroxychloroquine and chloroquine when these medicines are used on their own or in combination with the macrolide antibiotics azithromycin, clarithromycin or erythromycin.

The information and analyses contained in this report reflect evidence that was available at the time of the review in 2020. At time of publication in 2022 it has not been necessary to change the advice on the basis of newer evidence. The MHRA will continue to monitor the safety of all medicines. The information in this report will not be actively updated with new data or studies unless major new safety information is available that results in critical changes.

3. Background

A large observational study was published in August 2020 on the safety of hydroxychloroquine, alone and in combination with azithromycin, in patients with rheumatoid arthritis (Lane and colleagues, 2020).

Lane and colleagues reported increased cardiovascular mortality in association with long-term use (over 30 days on-treatment) of hydroxychloroquine, compared with sulfasalazine. This study also reported increased risks in a short term period (up to 30 days) of cardiovascular mortality, angina, and heart failure in association with hydroxychloroquine in combination with azithromycin, compared to hydroxychloroquine used in combination with amoxicillin.

Following the publication of the study by Lane, the MHRA conducted a review of these data, along with other evidence available up to November 2020, to understand whether there was a need to take any regulatory action.

Due to similarities in the safety profile between hydroxychloroquine and chloroquine, and between azithromycin and the other macrolides authorised in the UK (clarithromycin and erythromycin), available data for these medicines were also included in the review to understand if there were likely to be similar risks associated with chloroquine and with the other macrolide antibiotics.

Hydroxychloroquine and chloroquine

In the UK, hydroxychloroquine is indicated in adults for treatment of rheumatoid arthritis, discoid or systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight, and in children for juvenile idiopathic arthritis (in combination with other therapies), and discoid or systemic lupus erythematosus.

In the UK chloroquine is indicated for the prophylaxis, suppression, and treatment of malaria. Some chloroquine products also have indications for treatment of amoebic hepatitis and abscess, discoid and systemic lupus erythematosus, and rheumatoid arthritis.

Chloroquine and hydroxychloroquine are not authorised to treat COVID-19 related symptoms or prevent infection. At the time of this review, MHRA advice is that they should only be used for this purpose within a clinical trial.

Macrolide antibiotics

The three main macrolide antibiotics authorised and used in the UK are azithromycin, clarithromycin and erythromycin.

These macrolides have a similar antibacterial spectrum to penicillin and are frequently used as an alternative to penicillin, for example in patients allergic to penicillin:

- Azithromycin is indicated for respiratory tract infections (RTIs), otitis media, skin and soft tissue infections, urethritis, chlamydia and gonorrhoea
- Clarithromycin is indicated for RTIs, otitis media, skin and soft tissue infections and Helicobacter pylori eradication
- Erythromycin is indicated for RTIs, ear, eye and oral infections, skin and soft tissue infections, gastrointestinal infections and various other infections such as urethritis, chlamydia and gonorrhoea

Warnings on cardiovascular risks in the product information

At the time this review started, the UK product information for hydroxychloroquine and chloroquine contained warnings about the potential for cardiovascular adverse events, including QT interval prolongation, and the potential for interaction with other medicines known to cause QT prolongation. However, the product information for hydroxychloroquine and chloroquine did not specifically mention a potential interaction with macrolide antibiotics or contain any warnings about concurrent use of these medicines with macrolide antibiotics.

The product information for macrolide antibiotics contained warnings about the potential for cardiovascular adverse events, including QT prolongation, and the potential for interaction with other medicines known to cause QT prolongation. However, the product information for macrolide antibiotics did not specifically mention an interaction with hydroxychloroquine or chloroquine or contain any warnings about concurrent use with these medicines.

The MHRA review aimed to establish whether there was a need to take regulatory action to include the reported risks in the product information.

4. Epidemiological data from Lane and colleagues, 2020

This study (Lane and colleagues, 2020) was conducted across a multinational, distributed database network including primary and secondary care data from healthcare records and insurance claims databases in Germany, Japan, Netherlands, Spain, the UK (Clinical Practice Research Datalink (CPRD) and IQVIA Medical Research Data (IMRD)), and the USA. A cohort study design was used to investigate the safety of hydroxychloroquine, compared with sulfasalazine in patients with rheumatoid arthritis. The analysis also compared the safety of hydroxychloroquine in combination with azithromycin, to hydroxychloroquine in combination with amoxicillin.

Lane and colleagues used a short term analysis and a long-term (on-treatment) analysis. For the short term analysis, follow-up started 1 day after the index date and continued until the first of outcome of interest, loss to follow-up, or 30 days after the index date. For the longer-term, on-treatment analysis, follow up started 1 day after the index date and continued until the earliest of outcome of interest, loss to follow up, or discontinuation, with an added washout time of 14 days. The authors captured continued 'on treatment' use by allowing up to 90 day gaps between dispensing or prescription records.

As a secondary analysis, self-controlled case series (SCCS) was used to estimate the safety of hydroxychloroquine in the wider population, including for indications other than rheumatoid arthritis. For the new user cohort study, key predictors of exposure classification were selected for use in a propensity score, which was then used to stratify analyses to adjust for imbalance between exposure cohorts. For the secondary SCCS, many time-varying covariates including age, season, and other drug exposures were included in conditional Poisson regression models.

A total of 16 different severe adverse event outcomes were analysed. None of the safety outcomes studied appeared to be increased with the short term use of hydroxychloroquine compared with sulfasalazine in the 30 day analysis. Similar findings were seen with the long-term use of hydroxychloroquine compared with sulfasalazine, with the exception of cardiovascular mortality. The results for cardiovascular mortality in the long term on-treatment analysis appeared inconsistent across the available databases, with increased risk in two US databases but not in CPRD, but overall were increased in the hydroxychloroquine group when a meta-analysis was conducted: pooled hazard ratio (HR) 1.65 (95% confidence interval (CI) 1.12 to 2.44). Similar results were obtained in the SCCS analyses, which looked at the effect of hydroxychloroquine use (on-treatment versus off-treatment) on all outcomes (except mortality outcomes), regardless of indication.

In the cohort study analysis comparing hydroxychloroquine in combination with azithromycin to hydroxychloroquine in combination with amoxicillin, 3 severe adverse event outcomes appeared increased with the short term use of hydroxychloroquine in combination with azithromycin in meta-analysis: chest pain or angina (HR 1.15 (95% CI 1.05 to 1.26), heart failure (HR 1.22 (95% CI 1.02 to 1.45)), and cardiovascular mortality (HR 2.19 (95% CI 1.22 to 3.94)).

The paper from Lane and colleagues presents data on the largest available epidemiological study of the safety of hydroxychloroquine, with data primarily from the authorised indication of rheumatoid arthritis. The results are not necessarily generalisable to other patient populations. The results on the risk of severe adverse events associated with hydroxychloroquine treatment in the short term analysis are reassuring, with no excess risk for any of the considered safety outcomes compared with sulfasalazine. Longer term treatment with hydroxychloroquine, as used for rheumatoid arthritis, was associated with a 65% relative increase in cardiovascular mortality. However, it is noted that this finding is driven by the data from two US databases and the same risk was not seen in the study using the UK CPRD. The two US databases are larger, and hence powered to detect a smaller risk than the CPRD. However, there will also be differences in the data captured and populations covered which may have an impact on the findings. The CPRD is a primary care database, broadly representative of the UK population, while the two US databases are an insurance claims database (Clinformatics) and electronic healthcare data from a specific population of veterans (US Department of Veterans Affairs).

Furthermore, a significant risk was identified for users of hydroxychloroquine and azithromycin combined, with a 15% to 20% relative increase in the risk of angina or chest pain and heart failure and an approximately 2-fold relative increase in the risk of cardiovascular mortality in the 30 day short-term analysis. This risk might be anticipated based on the known cardiac toxicities of both products, possibly due to combined effects on QT interval, or by combined cardiotoxic effects more generally.

From a methodological perspective, this is a well-conducted study. As with all observational studies that make secondary use of data, there may be misclassification in terms of both exposure and outcome. The use of propensity score analyses to try and mitigate the impact of confounding is useful, but residual confounding and channelling bias may still occur. However, the general consistency of the results relating to small increases in cardiac risk to hydroxychloroquine in combination with azithromycin across the different cardiac-related outcomes and databases adds weight to the findings.

5. Other data on the cardiovascular safety of hydroxychloroquine or chloroquine, alone or in combination with azithromycin

In addition to the paper from Lane and colleagues, the MHRA reviewed data up to November 2020 from other published scientific studies and from the MHRA's UK Yellow Card database and the European EudraVigilance databases (up to October 2020). This review was to identify other relevant data on the safety of hydroxychloroquine or chloroquine used in their authorised indications and at their authorised doses, with or without the use of macrolides.

Findings by Sarayani and colleagues, 2020:

Sarayani and colleagues examined data from the FDA's Adverse Event Reporting System (FAERS) to determine whether there was a disproportionality of reporting of events of death and Torsades de Pointes (TdP) or QT prolongation for azithromycin, hydroxychloroquine, or chloroquine alone, as well as for hydroxychloroquine or chloroquine in combination with azithromycin, or for hydroxychloroquine or chloroquine in combination with amoxicillin (Sarayani and colleagues, 2020).

Proportional reporting ratios (PRR) were used as the measure of disproportionality. The PRR for azithromycin and TdP/QT prolongation was 4.10 (95% CI 3.80 to 4.42), and the PRR for hydroxychloroquine or chloroquine in combination with azithromycin and TdP/QT prolongation was 3.77 (95% CI 1.80 to 7.87). The authors concluded that azithromycin alone or when used with hydroxychloroquine or chloroquine was associated with a potential safety signal of TdP/QT prolongation. These data are consistent with the increased risk seen in the observational study by Lane and colleagues (2020).

The reporting of spontaneous adverse drug reactions (ADRs) may be influenced by a number of factors, for example awareness among healthcare professionals of the potential adverse drug reactions (ADRs) associated with certain medicines. Thus it is important not to over-interpret the results of this study, or to treat the PRR values as quantitative measures of the level of risk associated with different treatment combinations.

Findings by Cook and colleagues, 2006:

Cook and colleagues conducted a pharmacokinetic study to investigate a possible pharmacokinetic interaction between chloroquine and azithromycin (Cook and colleagues, 2006). In this study 40 healthy volunteers were assigned to receive azithromycin plus chloroquine (n=24) or chloroquine only (n=16). The rate of azithromycin absorption after administration of chloroquine was similar to that of azithromycin administered alone, and the authors reported that chloroquine had no clinically relevant effect on the pharmacokinetics of azithromycin.

This study adds to scientific knowledge relevant to the concomitant use of chloroquine and azithromycin. However these data are not considered to conflict with the evidence of a clinical impact on cardiac events when hydroxychloroquine and azithromycin were used concomitantly in the study by Lane and colleagues, as the mechanism could be a combined effect on QT interval, or by combined cardiotoxic effects more generally, rather than a pharmacokinetic interaction.

Data from spontaneous Adverse Drug Reaction reports

As part of this review, the MHRA searched the UK Yellow Card and European EudraVigilance databases of suspected adverse drug reactions for reports received up to October 2020 that might potentially indicate an interaction between hydroxychloroquine or chloroquine and macrolides.

The data from spontaneous ADR reports were limited and did not provide any substantial evidence to inform an assessment of the potential for interactions between hydroxychloroquine or chloroquine and macrolides when used in their authorised indications.

6. Discussion

At the time of this review, overall there were few published studies that investigated the safety of hydroxychloroquine and azithromycin when used concurrently in their authorised indications. This remains the case at time of publication in February 2022, and no new studies have been identified that alter the conclusions of this MHRA review.

The best source of evidence at the time of this report's publication remains that from the good-quality observational study by Lane and colleagues. This study provides evidence that using hydroxychloroquine with azithromycin compared to amoxicillin is associated with an increased risk of angina or chest pain and heart failure and of cardiovascular mortality in patients with rheumatoid arthritis. There is a plausible biological mechanism for such effects through possible combined effects on QT interval or through combined cardiotoxic effects more generally.

The other available published studies by Sarayani and colleagues and Cook and colleagues are consistent with such an effect, or at least do not conflict with it. Data from spontaneous ADR reports are too limited to be informative. Based on the strength of the evidence for harm when these medicines are used in combination, the outcome of the review was that product information should be updated to inform healthcare professionals of these risks.

Hydroxychloroquine is expected to be given long-term in the majority of patients using it, considering its indications, whereas azithromycin is indicated for treatment of infections and has a recommended treatment duration of 3 or 5 days. It is therefore anticipated that the most likely situation where these medicines might be used concomitantly would be where azithromycin is indicated for an infection occurring in a patient on existing long-term hydroxychloroquine treatment.

The infections that azithromycin is authorised to treat differ in terms of their seriousness. UK prescribing guidelines do not recommend azithromycin for community-acquired pneumonia or for acute exacerbations of chronic obstructive pulmonary disease. However, there is a possibility that for community-acquired pneumonia or other infections there may be patients for whom the antibiotics recommended by clinical guidelines are not effective or not tolerated and where azithromycin would represent an authorised and potentially effective treatment option.

A contraindication for concomitant use was considered during the MHRA review, but in view of these points, a contraindication is not warranted based on the current data. Therefore, the most appropriate regulatory action was to update to the product information for hydroxychloroquine and azithromycin products with the addition of information on the serious risks associated with their concomitant use. It is expected that healthcare professionals will take into account these risks when considering if there are any circumstances where the benefit of such concomitant use might outweigh the risks.

Direct evidence on the safety of the concomitant use of either hydroxychloroquine or chloroquine and the other macrolides authorised in the UK (clarithromycin and erythromycin) is lacking. However, hydroxychloroquine and chloroquine have similar safety profiles, and the macrolides also have similar safety profiles to each other. The potential for QT prolongation and cardiac adverse events is recognised in the product information for these medicines, which include specific warnings and contraindications for concomitant use of medicines that may prolong the QT interval. It was therefore considered appropriate to add the same warnings to the product information for chloroquine, clarithromycin, and erythromycin, making it clear that direct evidence is not available for chloroquine, clarithromycin, or erythromycin.

In terms of the safety data from the study by Lane and colleagues concerning the long-term use of hydroxychloroquine, there is a signal of increased cardiovascular mortality for hydroxychloroquine alone compared with sulfasalazine. This cardiovascular mortality increase was not seen consistently in the three databases for which cardiovascular mortality data were available, with an increased risk seen in data from two US databases but not that from CPRD. It is not possible to reach a firm conclusion on the reasons for this difference. Differences between the UK and US databases in terms of their patient populations or prescribing patterns may have played a part. It is also possible that this increased risk is present in the population represented by CPRD, but that it was not observed in this study due to lack of precision.

The UK product information for hydroxychloroquine includes cardiomyopathy in the list of potential adverse effects, with a statement that cardiomyopathy may result in cardiac failure and in some cases a fatal outcome. This wording is considered to remain an adequate description of the potential cardiac adverse effects, in view of the available data.

Data are lacking from the study by Lane and colleagues on whether there was any association between hydroxychloroquine and increased risks of mortality from other causes, compared with sulfasalazine. This study also did not provide any data on other disease-modifying treatments for rheumatoid arthritis.

It should be noted that this signal of increased cardiovascular mortality in association with long-term use is potentially less relevant for chloroquine, since the principal indications for chloroquine are for the prophylaxis, suppression, and treatment of malaria, and there is likely to be less long-term use of chloroquine than there is of hydroxychloroquine.

7. Conclusions

The conclusion of this review is that the product information is updated for medicines containing hydroxychloroquine or chloroquine, and medicines containing systemic macrolides (azithromycin, clarithromycin, erythromycin). The updates include a warning about the potential for adverse cardiovascular events when these medicines are used concomitantly.

No amendments to the product information are considered necessary for medicines containing topical macrolides (which are indicated for conjunctivitis or acne), as these products are used at lower doses and with very limited potential for systemic exposure. These medicines also do not list cardiovascular events as potential adverse effects associated with their use. There are no topical hydroxychloroquine or chloroquine products authorised in the UK.

No amendments to the hydroxychloroquine product information regarding cardiovascular risk when it is not used in combination with macrolides are considered necessary on the basis of the data from the study by Lane and colleagues and this review. This takes into consideration the existing warnings about the potential for cardiomyopathy, and the limitations of the study results raising a signal of potential excess cardiovascular mortality with long-term use of hydroxychloroquine compared with sulfasalazine.

The updates have been implemented in the product information and are presented in the Annexes of this report.

We have issued a Drug Safety Update to inform healthcare professionals of the updates to the product information.

8. References

Cook JA and others. Lack of a pharmacokinetic interaction between azithromycin and chloroquine. The American Journal of Tropical Medicine and Hygiene 2006: volume 74, pages 407 to 12.

Lane JCE and others. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study 2020. The Lancet Rheumatology 2020: volume 2, pages 698 to 711.

Sarayani A and others. Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine. Research in Social & Administrative Pharmacy 2020: volume 17, pages 483 to 86.

9. Glossary of Terms

Adverse drug reaction
A suspected side effect of a medicine.

Cohort study
In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between 2 groups, and usually accompany ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between 2 groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Epidemiological studies
Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

Hazard ratio
One measure of risk. Hazard ratios estimate the risk for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk.

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Observational study
A type of research study where data on health outcomes are collected and analysed, without changing what treatments or procedures people receive.

Poisson regression
Poisson regression is a statistical method that attempts to determine the strength and character of the relationship between one dependent variable and a series of other variables.

Pharmacodynamics
Pharmacodynamics describes the effects a medicine has on the body.

Pharmacokinetics
Pharmacokinetics describes how the human body affects a medicine, such as , how the medicine is absorbed, chemical changes the medicine undergoes, how the medicine moves through the body and is eventually removed from the body.

QT prolongation
A heart condition that affects how the heart beats. Some people with QT prolongation will not have symptoms, but some may experience light-headedness, fainting, or heart palpitations. In some people, QT prolongation can lead to the heart stopping beating (cardiac arrest).

Self-controlled case series
A type of study where health outcomes are compared for each study participant in the time before they are exposed to some event (such as taking a medicine) and in the time after they are exposed to it. This is a way of being able to measure the effects of the exposure in a way that is not affected by other factors (like whether a person has a certain genetic makeup) because these stay the same for each person before and after the exposure.

Torsades de Pointes
An abnormal heart rhythm that can result in sudden cardiac death. It is usually associated with QT prolongation.

Yellow Card scheme
The MHRA’s scheme for healthcare professionals and members of the public to report suspected adverse reactions for a medicine or vaccine, as well as medical devices and other products.

10. Annexes

List of Annexes:

Annex 1: Product information updates for medicines containing hydroxychloroquine

Hydroxychloroquine products

These apply to all authorised medicines in the UK that include hydroxychloroquine.

SPC section 4.4

Carefully consider the benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin or other macrolide antibiotics, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

SPC section 4.5 (under an appropriate subheading if section 4.5 includes subheadings based on the interacting medicines or the type of interaction)

Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin. Similar careful consideration of the balance of benefits and risks should also be undertaken before prescribing hydroxychloroquine for any patients taking other macrolide antibiotics, such as clarithromycin or erythromycin, because of the potential for a similar risk when hydroxychloroquine is co-administered with these medicines.

Patient Information Leaflet

Section 2. What you need to know before you take <product name/INN> (to be included as a bullet point under the appropriate subheading, e.g. “Taking other medicines”, “Other medicines and <product name/INN>”, etc.)

- Some antibiotics used for infections (such as azithromycin, clarithromycin, erythromycin, gentamicin, neomycin or tobramycin). Taking azithromycin, clarithromycin, or erythromycin at the same time as hydroxychloroquine may increase the chance of you getting side effects that affect your heart.

Annex 2: Product information updates for medicines containing chloroquine

Chloroquine products

These apply to all authorised medicines in the UK that include chloroquine.

SPC section 4.4

Carefully consider the benefits and risks before prescribing chloroquine for any patients taking macrolide antibiotics, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

SPC section 4.5 (under an appropriate subheading if section 4.5 includes subheadings based on the interacting medicines or the type of interaction)

Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because similar risks may potentially be present with chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing chloroquine for any patients taking azithromycin or other macrolide antibiotics, such as clarithromycin or erythromycin.

Patient Information Leaflet

Section 2. What you need to know before you take <product name/INN> (to be included as a bullet point under the appropriate subheading, e.g. “Taking other medicines”, “Other medicines and <product name/INN>”, etc.)

- Azithromycin, clarithromycin, or erythromycin (antibiotics used for treating infections). Taking these medicines at the same time as chloroquine may increase the chance of you getting side effects that affect your heart.

Annex 3: Product information updates for medicines containing azithromycin

Azithromycin products

These apply to all authorised medicines in the UK that include azithromycin administered systemically (oral or intravenous use).

SPC section 4.4

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

SPC section 4.5 (under an appropriate subheading if section 4.5 includes subheadings based on the interacting medicines or the type of interaction)

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

Patient Information Leaflet

Section 2. What you need to know before you take <product name/INN> (to be added as a bullet point under the appropriate subheading, e.g. “Taking other medicines”, “Other medicines and <product name/INN>”, etc.)

- Hydroxychloroquine or chloroquine (used to treat conditions including rheumatoid arthritis, or to treat or prevent malaria): Taking these medicines at the same time as azithromycin may increase the chance of you getting side effects that affect your heart.

Annex 4: Product information updates for medicines containing clarithromycin or erythromycin

<Clarithromycin/Erythromycin> products (delete as applicable)

These apply to all authorised medicines in the UK that include clarithromycin or erythromycin administered systemically (oral or intravenous use).

SPC section 4.4

Carefully consider the balance of benefits and risks before prescribing <clarithromycin/erythromycin> for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

SPC section 4.5 (under an appropriate subheading if section 4.5 includes subheadings based on the interacting medicines or the type of interaction)

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing <clarithromycin/erythromycin> for any patients taking hydroxychloroquine or chloroquine.

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Alternative format versions of this report are available on request from info@mhra.gov.uk.