Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for clarithromycin, the scientific conclusions are as follows:

In view of available data on an increased risk of cardiac arrhythmia and serious cardiovascular adverse events following concomitant use of chloroquine/hydroxychloroquine and the macrolide antibiotic azithromycin from a literature publication of Lane et al (2020), and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between clarithromycin and an increased risk of cardiac arrhythmia and serious cardiovascular adverse events with concomitant use of hydroxychloroquine or its parent compound, chloroquine is at least a reasonable possibility.

In view of available data on a pharmacokinetic interaction with edoxaban from the literature and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between clarithromycin and an increased risk of bleeding with the direct acting oral anti-coagulant edoxaban is at least a reasonable possibility.

In view of available data on an interaction with ivabradine based on a plausible mechanism of action, the PRAC considers that a causal relationship between clarithromycin and an interaction with ivabradine is at least a reasonable possibility.

In view of available data on an interaction with systemic or inhaled corticosteroids from the literature and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between clarithromycin and increased systemic exposure to corticosteroids is at least a reasonable possibility.

The PRAC concluded that the product information of clarithromycin-containing products should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisations

On the basis of the scientific conclusions for clarithromycin, the CMDh is of the opinion that the benefit-risk balance of the medicinal products containing clarithromycin is unchanged, subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisations should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal products

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.3 Contraindications

The contraindication should be amended as follows:

[…]

Concomitant administration with ticagrelor, **ivabradine** or ranolazine is contraindicated.

- Section 4.4 Special warnings and precautions for use

The warning should be amended as follows:

Oral anticoagulants

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban**,** ~~and~~ apixaban **and edoxaban**, particularly to patients at high risk of bleeding (see section 4.5).

- Section 4.5 Interaction with other medicinal products and other forms of interaction

An interaction should be added as follows:

Hydroxychloroquine and chloroquine: Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

Interactions should be updated/added as follows:

Direct acting oral anticoagulants (DOACs)

The DOAC**s** dabigatran **and edoxaban are** ~~is a~~ substrate**s** for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

[…]

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor**, ivabradine** and ranolazine (see section 4.3).

[…]

Corticosteroids

Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

Package Leaflet
Section 2. What you need to know before you take [product name]

Do not take X if:

[…]

- you are taking medicines called ticagrelor**, ivabradine** or ranolazine (for angina or to reduce the chance of heart attack or stroke)

[…]

Other medicines and <X>

Tell your doctor or pharmacist if you are taking any of the following medicines:

[…]

Warfarin or any other anticoagulant e.g. dabigatran, rivaroxaban, apixaban, **edoxaban** (used to thin your blood).

[…]

This is also important if you are taking medicines called:

• **hydroxychloroquine or chloroquine (used to treat conditions including rheumatoid arthritis, or to treat or prevent malaria). Taking these medicines at the same time as clarithromycin may increase the chance of getting abnormal heart rhythms and other serious side effects that affect your heart**

[…]

• **corticosteroids, given by mouth, by injection or inhaled (used to help suppress the body's immune system - this is useful in treating a wide range of conditions)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	01 February 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 March 2024