Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

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

Exposure during pregnancy

In view of available data on overall major congenital malformations following in utero exposure from observational studies, the PRAC considers that information about the overall risk of major congenital malformations should be provided. The PRAC concluded that the product information of products containing erythromycin (systemic formulations) should be amended accordingly.

Drug interaction with Corticosteroids

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 a causal relationship between erythromycin and increased systemic exposure to corticosteroids is at least a reasonable possibility. The PRAC concluded that the product information of products containing erythromycin (systemic formulations) should be amended accordingly.

Interaction with Lomitapide

In view of available data on an interaction with lomitapide from the literature, the labelling of other macrolides (clarithromycin) and lomitapide, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between erythromycin and markedly increased transaminases with lomitapide is at least a reasonable possibility. The PRAC concluded that the product information of products containing erythromycin (systemic formulations) should be amended accordingly.

Interaction with Chloroquine/Hydroxychloroquine

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 the recent literature publication of Lane et al (2020), and in view of a plausible mechanism of action, the PRAC considers a causal relationship between erythromycin 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. The PRAC concluded that the product information of products containing erythromycin (systemic formulations) should be amended accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for erythromycin (systemic use) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing erythromycin (systemic use) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing erythromycin (systemic use) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

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

Exposure during pregnancy

Summary of Product Characteristics

- Section 4.6

New information with regards to the risk(s) of the product when used during pregnancy should be added as follows (new text **underlined and in bold**, deleted text ~~strike through~~):

Pregnancy

~~There are no adequate and well-controlled studies in pregnant women.~~ **The available epidemiological studies on the risk of major congenital malformations with use of macrolides including erythromycin during pregnancy provide conflicting results.** ~~However,~~ **Some** observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.

Erythromycin has been reported to cross the placental barrier in humans, but foetal plasma levels are generally low.

There have been reports that maternal macrolide antibiotics exposure within 10 weeks of delivery may be associated with a higher risk of infantile hypertrophic pyloric stenosis (IHPS).

Erythromycin should be used by women during pregnancy only if clearly needed.

[…]

Package Leaflet

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

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

The active ingredient of [product name] may cross the placenta in pregnant women and is excreted in breast milk. **Information from studies regarding the risk of birth defects is inconsistent, but some studies have reported heart defects following <product name> use in early pregnancy.**

Erythromycin should be used by women during pregnancy or while breast-feeding only if clearly needed.

Drug interaction with Corticosteroids

The following changes to the product information of medicinal products containing the active substance erythromycin (systemic formulations) are recommended (new text **underlined and in bold**):

Summary of Product Characteristics

- Section 4.5

An interaction should be added as follows:

Corticosteroids

Caution should be exercised in concomitant use of erythromycin 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]

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including any medicines obtained without a prescription.

[…]

This is also important if you are taking medicines called:

[…]

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);

Interaction with Lomitapide

The following changes to the product information of medicinal products containing the active substance erythromycin (systemic formulations) are recommended (new text **underlined and in bold**):

Summary of Product Characteristics

- Section 4.3

The contraindication should be added as follows:

[…]

Concomitant administration of erythromycin and lomitapide is contraindicated (see section 4.5).

- Section 4.5

An interaction should be added as follows:

HMG-CoA Reductase Inhibitors: Erythromycin is contraindicated in patients receiving the HmG-CoA reductase inhibitors lovastatin and simvastatin (see section 4.3). Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Concomitant administration of erythromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

Package Leaflet

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

Do not take [product name]:

•if you are currently taking a medicine called:

-lomitapide (used to lower increased blood fats such as cholesterol and triglycerides). Taking this medicine at the same time as erythromycin may lead to a rise in enzymes produced by liver cells (transaminases), which indicates that the liver is under stress and may lead to liver problems.

Interaction with Chloroquine/Hydroxychloroquine

The following changes to the product information of medicinal products containing the active substance erythromycin are recommended (new text **underlined and in bold**):

Summary of Product Characteristics

- Section 4.5

An interaction should be added as follows:

Hydroxychloroquine and chloroquine: Erythromycin 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.

Package Leaflet

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

[…]

Other medicines and <X>

[…]

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 erythromycin may increase the chance of getting abnormal heart rhythms and other serious side effects that affect your heart.

Annex III

Timetable for the implementation of this position

[

Timetable for the implementation of this position

Adoption of CMDh position:	10 November 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	04 January 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	23 February 2023