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 clarithromycin, the scientific conclusions are as follows:

In view of available data on an increased risk of bleeding with Direct Acting Oral Anti-coagulants (DOACs) from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between clarithromycin and an increased risk of bleeding with Direct Acting Oral Anti-coagulants is at least a reasonable possibility. The PRAC concluded that the product information of products containing clarithromycin should be amended accordingly.

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

In view of available data on an increased risk of QT prolongation in patients with hypomagnesaemia from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between clarithromycin and an increased risk of QT prolongation in patients with hypomagnesaemia is at least a reasonable possibility. The PRAC concluded that the product information of products containing clarithromycin should be amended accordingly.

In view of available data on malformations, miscarriage and exposure through breast milk from the literature, the PRAC considers that information about the risk of miscarriage and malformations and the exposure through breast milk should be provided. The PRAC concluded that the product information of products containing clarithromycin 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 clarithromycin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing clarithromycin 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 clarithromycin 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 **<u>underlined and in bold</u>**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Oral anticoagulants

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

- Section 4.5

The interaction should be added as follows:

Effect of clarithromycin on Other Medicinal Products

Oral anticoagulants (e.g. warfarin**<u>, rivaroxaban, apixaban</u>**)

<u>Direct acting oral anticoagulants (DOACs)</u>

<u>The DOAC dabigatran is a substrate 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).</u>

Package Leaflet

- Section 2 What you need to know before you take X

Other Medicines and X

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

……

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

Summary of Product Characteristics

- Section 4.3

A contraindication should be added as follows:

<u>Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).</u>

- Section 4.5

An interaction should be added as follows:

<u>Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases (see section 4.3).</u>

Package Leaflet

- Section 2. What you need to know before you take X

Do not take X if:

……..

You are taking a medicine containing lomitapide

Summary of Product Characteristics

- Section 4.3

A contraindication should be amended/added as follows:

Clarithromycin should not be given to patients with **electrolyte disturbances** ~~hypokalaemia~~ (**hypokalaemia or hypomagnesaemia, due to the** risk of prolongation of **the** QT **interval** ~~time~~).

- Section 4.4

Cardiovascular Events

A warning should be removed as follows:

~~Patients with hypomagnesaemia;~~

Package Leaflet

- 2. What you need to know before you take clarithromycin tablets

Do not take X if:

……..

-You have abnormally low levels of potassium **or magnesium** in your blood (hypokalaemia **or hypomagnesaemia**)

Warnings and Precautions

Talk to your doctor, pharmacist or nurse before taking X:

…….

~~-If you have abnormally low levels of magnesium in your blood (hypomagnesaemia)~~

Summary of Product Characteristics

- Section 4.6

Text should be amended/added as follows:

Pregnancy

The safety of clarithromycin for use in pregnancy has not been established. Based on variable results obtained from **animal** studies ~~in mice, rats, rabbits and monkeys,~~**and experience in humans,** the possibility of adverse effects on embryofoetal development cannot be excluded. **Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results.**

Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk**s**.

Breast-feeding

…

Clarithromycin is excreted into human breast milk **in small amounts**. **It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	24 January 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 March 2021