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:

Epidemiological studies available during the reporting period have investigated the risk of adverse cardiovascular outcomes with macrolides. Results from these studies are variable; however, some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Given the extent of the research conducted in the area and the extensive market exposure to clarithromycin, PRAC considered an update to section 4.4 of the Summary of Product Characteristics for clarithromycin containing products is warranted so as to allow healthcare professionals to consider the epidemiological findings in the context of the known treatment benefits of clarithromycin.

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 **underlined and in bold,** deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A new warning should be added as follows:

~~*Prolongation of the QT Interval*~~ ***Cardiovascular Events***

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes), clarithromycin should be used with caution in the following patients;

- *Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia,*
- *Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia (see section 4.3).*
- *Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5).*
- *Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).*
- *Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).*

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 January 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 March 2018