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, the scientific conclusions are as follows:

Cardiovascular Risk
Based on the totality of the evidence, including data from meta-analyses, it is recommended that the product information for erythromycin containing products should be updated in line with the PRAC recommendation for clarithromycin. There is merit in reflecting the increased short term risk of adverse CV outcomes reported in observational studies in the product information so that the benefits and risks of treatment in individual patients, particularly those at high risk of CV events, can be fully evaluated by HCPs at the time of treatment initiation.
Given the known risk of QT prolongation with macrolides and in order to align with the product information of clarithromycin, MAHs should update section 4.3 of the SmPC to reflect that erythromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmia and that it should not be given to patients with electrolyte disturbances due to the risk of QT prolongation. Updates to section 4.8 to include ventricular fibrillation and cardiac arrest are recommended based on multiple reported cases and a clear mechanistic bases.

Infantile Pyloric Stenosis
There is consistent evidence across a reasonable body of literature to support an association between exposure to erythromycin in infants and the risk of IHPS. Data from three meta-analyses suggest a 2-3-fold increase in the risk of IHPS in infants particularly during the first 14 days of life. Based on this data the updates to the product information outlined below are suggested.

Increased risk of bleeding following drug interaction with Rivaroxaban
A signal of increased risk of bleeding following a drug interaction between rivaroxaban and macrolide antibiotics was discussed at PRAC for analysis and prioritisation in September 2017 and resulted in updates to the product information of Rivaroxaban. The SmPC for erythromycin does not make any reference to the novel direct acting oral anticoagulants therefore an update to section 4.5 of the SmPC to additionally reflect rivaroxaban is recommended.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing erythromycin which are systemically absorbed were warranted.

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 the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing erythromycin 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 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

1. Cardiovascular Risk

Section 4.3

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Erythromycin is contraindicated in patients taking astemizole, terfenadine, domperidone, cisapride or pimozide
Erythromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5)
Erythromycin should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval)

Section 4.4

~~QT Prolongation~~ **Cardiovascular Events**
~~Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during post marketing surveillance in patients receiving erythromycin.~~
Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including erythromycin (see sections 4.3, 4.5 and 4.8).
Fatalities have been reported.

Erythromycin should be used with caution in the following;
Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.
Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.3 and 4.5)
~~Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.~~ Elderly patients may be more susceptible to drug- associated effects on the QT interval (see section 4.8).
~~Patients receiving erythromycin concurrently with drugs which can cause prolongation of the QT interval should be carefully monitored. The concomitant use of erythromycin with some of these drugs is contraindicated (see sections 4.3 & 4.5)~~
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 erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.

Section 4.8

Cardiac disorders SOC
Cardiac arrest, ventricular fibrillation (frequency not known)

2. Infantile Pyloric Stenosis

Section 4.4

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. **Epidemiological studies including data from meta-analyses suggest a 2-3-fold increase in the risk of IHPS following exposure to erythromycin in infancy. This risk is highest following exposure to erythromycin during the first 14 days of life. Available data suggests a risk of 2.6% (95% CI: 1.5 -4.2%) following exposure to erythromycin during this time period. The risk of IHPS in the general population is 0.1-0.2%.** ~~In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious, vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy.~~ Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

3. Increased risk of bleeding following drug interaction with Rivaroxaban

Section 4.5

"There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g. warfarin, **rivaroxaban**) are used concomitantly'.

Package Leaflet

1. Cardiovascular Risk

Section 2 Do not take Erythromycin:

>If you are currently taking a medicine called:
-terfenadine or astemizole (widely taken for hayfever and allergies), cisapride (for stomach disorders) or pimozide (for psychiatric conditions) while receiving erythromycin, as combining these drugs can sometimes cause serious disturbances in heart rhythm. Consult your doctor for advice on alternative medicines you can take instead;
>You have abnormally low levels of potassium or magnesium in your blood (hypomagnesaemia or hypokalaemia)
>You or someone in your family has a history of heart rhythm disorders (ventricular cardiac arrhythmia or torsades de pointes) or an abnormality of the electrocardiogram (electrical recording of the heart) called "long QT syndrome".
Warnings and Precautions
>You are taking other medicines which are known to cause serious disturbances in heart rhythm
>If you have heart problems

Section 4 Possible Side effects
Abnormal heart rhythms (including palpitations, a faster heartbeat, a life-threatening irregular heart beat **called torsades de pointes** or abnormal ECG heart tracing) **or heart stopping (cardiac arrest)**;

2. Increased risk of bleeding following drug interaction with Rivaroxaban

Section 2

Other medicines and Erythromycin
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:
- ~~warfarin and acenocoumarol~~ **Anticoagulants e.g. warfarin, acenocoumarol and rivaroxaban (used to thin the blood)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	03 January 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 February 2020