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 quinine, the scientific conclusions are as follows:

Atrioventricular block

Taking into consideration results from a population based retrospective cohort study (Gjesing et al. 2015), which found an increased risk of all-cause and of cardiovascular mortality in quinine users with heart failure also taking beta blockers, and the fact that quinine is an isomer of quinidine, a class 1a antiarrythmic which reduces the velocity of cardiac conduction the PRAC found it biologically plausible that quinine could aggravate atrioventricular block. PRAC therefore recommends the update of section 4.4. of the SmPC to reflect that quinine should be used with caution in patients with atrioventricular block.

QT prolongation

Quinine is well known to have dose-dependent effects on the QT interval. Two studies (Gjesing et al 2015, Sheehan et al. 2016) highlighted the potential for cardiac toxicity even at therapeutic doses of quinine in patients with multiple risk factors for QT prolongation.

Sections 4.4 and 4.5 of the SmPCs should therefore be updated to add a warning on dose-dependent QT prolonging effects.

Interaction with carbamazepine and phenobarbital (resulting in increased anticonvulsant levels)

The results of the pharmacokinetics study conducted in healthy volunteers using an open-label prospective crossover design showed that quinine increased Cmax (Maximum concentration observed) and AUC (area under the concentration time curve) of carbamazepine and phenobarbital. Significantly increased urinary recovery of both medicinal products has been also observed.

An interaction with carbamazepine in terms of inhibition by quinine of CYP3A4, and with phenobarbital in terms of inhibition by quinine of P-gp, is biologically plausible.

The PRAC considers that the above information is relevant and therefore recommends the update of section 4.5 of the SmPCs to reflect this information.

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 quinine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing quinine 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 quinine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 warning should be added as follows:

Cardiac disorders

Quinine has dose-dependent QT-prolonging effects. Caution is recommended in patients with conditions which predispose to QT-prolongation and in patients with atrioventricular block.

- Section 4.5

Caution is advised when administering quinine with drugs which could prolong the QT interval.

Quinine may increase the levels of phenobarbital and of carbamazepine. Patients should be monitored closely during concomitant use of quinine with these agents.

Package Leaflet

- Section 2

Section 2

Tell your doctor if you were born with or have any condition that causes an abnormal heart rhythm.

Tell your doctor if you are taking:

- **Medicines which are known to cause disturbances in heart rhythm.**
- **Barbiturates or carbamazepine (medicines to treat epilepsy).**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

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