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 mefloquine, the scientific conclusions are as follows:

PRAC noted that both abnormal dreams and insomnia are listed as very common ADRs in section 4.8 of the summary of product characteristics (SmPC) but only abnormal dreams is included in the 'boxed warning' in section 4.4 of the SmPC. Based on a publication published during the reporting period, PRAC considered that insomnia appears as likely as abnormal dreams to be a prodromal event for a neuropsychiatric adverse event in a patient taking mefloquine. The PRAC concluded that sections 4.4 and 4.8 of the SmPC should therefore be amended to add insomnia. The Package Leaflet is updated 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 mefloquine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing mefloquine 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 mefloquine 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

The boxed warning should be revised as follows:

Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as **insomnia**, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event (see section 4.8). Cases of suicide, suicidal thoughts and self-endangering behaviour such as attempted suicide (see section 4.8) have been reported.

- Section 4.8

The following text should be revised as follows:

Sleep disturbances and abnormal dreams/nightmares

Abnormal dreams **and insomnia** are very common adverse reactions with mefloquine, therefore their significance should be considered in the overall evaluation of patients reporting reactions or changes to their mental state with mefloquine (see boxed warning section 4.4).

Package Leaflet

- Section 2. What you need to know before you use mefloquine

The section should be revised as follows:

Mefloquine can cause serious psychiatric problems in some patients. Inform your physician immediately if you experience any of the following symptoms during treatment with mefloquine:

...
- **insomnia**
...

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	23 December 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	21 February 2018