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 artemether / lumefantrin (apart from the dispersible tablet), the scientific conclusions are as follows:

Three literature articles (Kurth et al. 2016, Nakajima-Ushijama et al. 2018, Merat et al. 2003 cover 6 subjects, that developed hemolytic anemia after treatment with artemether/lumefantrine.

The MPA performed a search in EudraVigilance and detected 15 cases of haemolytic anemia, including delayed haemolytic anemia, that are at least possibly related to malaria treatment with artemether/lumefantrine only, thereof 7 cases with non-severe malaria. In five of those there is sufficient information to conclude that AL cannot be ignored as possible explanation. The 15 cases identified in the Eudravigilance database comprises amongst others cases described by Nakajima-Ushijama et al. 2018.

In view of available data on delayed hemolytic anemia in connection to treatment with artemether/lumefantrine from the literature, spontaneous reports including 5 cases identified in non-severe malaria and in view of a plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between artemether/lumefantrine and delayed hemolytic anemia is at least a reasonable possibility. Given that asymptomatic anemia will not be treated, and in an European setting, a patient treated for malaria will be followed up after treatment, including with blood sampling, no warning statement is considered warranted. Therefore, the PRAC concludes that the product information of products containing artemether/lumefantrine should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction delayed hemolytic anemia with a frequency unknown. 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 artemether / lumefantrin (apart from the dispersible tablet) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing artemether / lumefantrin (apart from the dispersible tablet) 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 artemether / lumefantrin (apart from the dispersible tablet) 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 4.8

The following adverse reaction should be added under the SOC Blood and lymphatic system disorders with a frequency unknown:

Delayed haemolytic anaemia*

Footnote
* **Has been reported up to a few weeks after treatment has been stopped**

Package Leaflet

- Possible side effects

Not known (frequency cannot be estimated from the available data)

Anaemia due to breakdown of red blood cells, which has been reported up to a few weeks after treatment has been stopped (delayed haemolytic anaemia).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 July 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 September 2020