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 hydroxychloroquine, the scientific conclusions are as follows:

In view of available data on sweet's syndrome from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between hydroxychloroquine and sweet's syndrome is at least a reasonable possibility. Furthermore, since several severe cutaneous adverse reactions (SCARs) are listed in section 4.8 of the SmPC, a corresponding warning should be also added. The PRAC concluded that the product information of products containing hydroxychloroquine should be amended 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 hydroxychloroquine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing hydroxychloroquine 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 hydroxychloroquine 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 warning should be added as follows:

Severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse drug reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with hydroxychloroquine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. If signs and symptoms suggestive of severe skin reactions appear, hydroxychloroquine should be withdrawn at once and alternative therapy should be considered.

- Section 4.8

The following adverse reaction(s) should be added under the *SOC Skin and subcutaneous tissue disorders* with a frequency *Not known*:

Erythema multiforme, photosensitivity, exfoliative dermatitis, **Sweet's syndrome and Severe cutaneous adverse reactions (SCARs)** including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), see section 4.4. AGEP has to be distinguished from psoriasis, although hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favourable after hydroxychloroquine withdrawal.

Package Leaflet

- Section 2

A warning should be added as follows:

Serious skin rashes have been reported with the use of hydroxychloroquine (see section 4 possible side effects). Frequently, the rash can involve ulcers of the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). These serious skin rashes are often preceded by flu-like symptoms such as fever, headache and body ache. The rash may progress to widespread blistering and peeling of the skin. If you develop these skin symptoms, stop taking hydroxychloroquine and contact your doctor immediately.

- Section 4

Stop taking [product name] and see a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

[…]

- **Severe skin reactions (see section 2 Warnings and precautions) such as:**

- **rash with a fever and flu-like symptoms and enlarged lymph nodes. This could be a condition called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).**
- **blistering, widespread scaly skin, pus-filled spots together with fever. This could be a condition called Acute Generalized Exanthematous Pustulosis (AGEP).**
- **blistering or peeling of the skin around the lips, eyes, mouth, nose and genitals, flu-like symptoms and fever. This could be a condition called Stevens-Johnson syndrome (SJS)**
- **multiple skin lesions, itching of the skin, joint aches, fever and a general ill feeling. This could be a condition called Toxic Epidermal Necrolysis (TEN)**
- **skin reaction including plum-colored, raised, painful sores, particularly on your arms, hands, fingers, face and neck, which may also be accompanied by fever. This could be a condition called Sweet syndrome**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 January 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 March 2022

APPENDIX I

PRAC PSUR Assessment Report