I.12 (item number)	Hydroxychloroquine - Cutaneous lupus erythematosus (application title)
Does the application adequately address the issue of the public health need for the medicine?	■ Yes ☐ No ☐ Not applicable Comments: *The incidence of CLE ranges from 2.59 to 4.3 cases per 100,000 persons per year, and in its active form may lead to damage (dyspigmentation and/or scarring) and is associated with considerable morbidity and quality of life impairment*.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	*The therapeutic agent for CLE presented in 21st WHO Model List of Essential Medicines (2019) (pg.38, section 13) is limited to topical corticosteroids. However, because of cutaneous side effects, including atrophy, telangiectasia, and steroid-induced rosacea-like dermatitis, it is recommended that treatment with topical corticosteroids be intermittent and not exceed a treatment duration of a few weeks.*
Have all important studies and all relevant evidence been included in the application?	☐ Yes ■ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included *A Cochrane Systematic Review [Hannon 2021] was recently published (21 March 2021) and therefore was not included in the application.*
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	■ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). • *HCQ demonstrated efficacy against placebo in the treatment of CLE* • *HCQ is associated with similar efficacy and better safety profile than acitretin in the treatment of CLE* • *HCQ is associated with a better safety profile than CQ particularly for the risk of retinopathy* • *In SLE, HCQ is associated with a decreased risk of flare, decreased risk of damage and an improved survival* Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? • *In common with other medications there is little data on the use of HCQ in*

	pregnancy in patients with CLE or other diseases. But current national guidelines e.g. NICE (https://bnf.nice.org.uk/drug/hydroxychloroquine-sulfate.html) recommend that users follow the manufacturer guidance and avoid the use of the medicine in pregnant women unless necessary on health grounds. • *A recent analysis of childbirth outcomes for women taking HCQ confirms this advice. It compared pregnant women receiving HCQ with the general population and showed a low risk in the first trimester of pregnancy. Overall, 54.8 per 1000 infants exposed to hydroxychloroquine were born with a major congenital malformation versus 35.3 per 1000 unexposed infants, corresponding to an unadjusted relative risk of 1.51. There were increases in the risk of oral clefts, respiratory anomalies, and urinary defects, although the authors state that estimates were imprecise. No pattern of malformation was identified*
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	■ Yes ☐ No ☐ Not applicable Comments: • *Based on the result of a systematic review, the frequency of adverse events reported in all the studies with HCQ has been low, mainly gastrointestinal and cutaneous, usually mild* • *In a meta-analysis, the prevalence of retinopathy was 2.5% with CQ versus 0.1% with HCQ* • *The most common severe adverse events of HCQ is retinopathy. For daily consumption of 4.0 to 5.0 mg/kg, the prevalence of retinal toxicity remained less than 2% within the first 10 years*
Are there any adverse effects of concern, or that may require special monitoring?	■ Yes ☐ No ☐ Not applicable Comments: *Retinal toxicity is the most severe adverse event associated with HCQ. Based on the American Academy of Ophthalmology guidelines, in the absence of risk factors for retinal toxicity, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter.*
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	*The overall benefit-risk ratio is favourable to the intervention. Although some uncertainties remain on the efficacy/effectiveness, this is a relatively safe intervention and has been widely used with this therapeutic purpose for decades.*
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	*The overall quality/certainty of evidence is low to moderate for relevant outcomes (the certainty was downgraded due to imprecision: small sample size/number of events).*

Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	■ Yes ☐ No ☐ Not applicable Comments: *It is worthy of highlighting that because of uncertainty in the safeness of hydroxychloroquine in pregnancy, some agencies have recommended that pregnant women should use this intervention only in the presence of an imperative health need (https://bnf.nice.org.uk/drug/hydroxychloroquine-sulfate.html).*
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ■ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ■ No ☐ Not applicable Comments: *no guideline for CLE was found.*
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	*There is limited data for comparative cost evaluation and cost-effectiveness of hydroxychloroquine for CLE.* *It is reasonable to assume that hydroxychloroquine is relatively affordable and widely diffused, as this intervention is being used/recommended for different communicable and non-communicable diseases for decades.* *The applicant presented a raw cost estimate of hydroxychloroquine in different countries:* *<u>300mg tabs</u>* *UK: Range £ 5.10 - £32.49 for 60 tablets* *US: Range $ 37.22 – $110.64 for 100 tablets* *Australia: AusD 26.08 for 100 tablets* *Canada: range $ 39.88- 119.42* *Costa Rica: - $8.80 100 tablets* *<u>200mg tabs</u>* *Eastern Caribbean States: 9 $ for 100 tablets*
Any additional comments	----

Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	*Considering:* *(a) the favourable overall benefit to risk ratio of hydroxychloroquine* *(b) the probable affordability and reasonable access* *(c) its role in the care of CLE patients.* *A favourable recommendation to include hydroxychloroquine on the EML is possible.* *Therefore, the proposed recommendation to the Expert Committee is to **incorporate** hydroxychloroquine **on the EML.***
References (if required)	*Hannon CW, McCourt C, Lima HC, Chen S, Bennett C. Interventions for cutaneous disease in systemic lupus erythematosus. Cochrane Database Syst Rev. 2021 Mar 9;3(3):CD007478. doi: 10.1002/14651858.CD007478.pub2.*