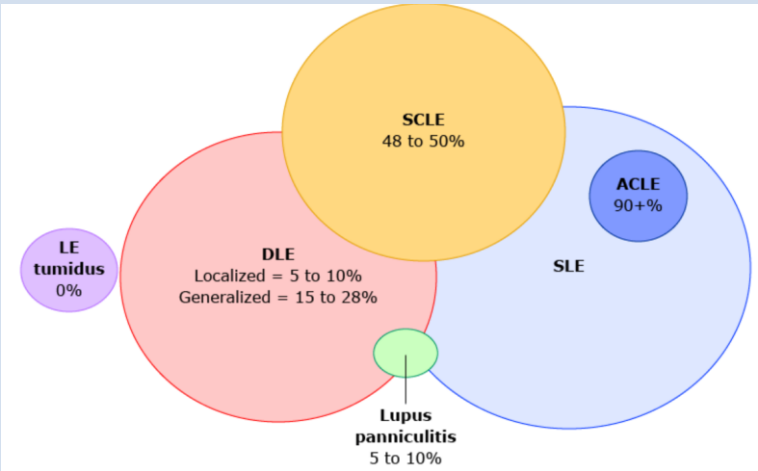
I.12	Hydroxychloroquine for cutaneous lupus erythematosus
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can cause inflammation throughout the body, including the skin. Cutaneous disease is common in SLE; approximately 80 percent of patients develop skin disease at some point in their disease course. However, cutaneous LE (CLE) frequently exists independently of SLE and may be two to three times more prevalent than SLE. Worldwide, subacute CLE prevalence ranges from 17-48 cases per 100,000 persons. A nationwide registry-based cohort study was conducted in Denmark from 1998 to 2013 reported an annual incidence rate of CLE of 2.74/100,000 with a female:male ratio of 4:1 (Prütz Petersen 2018). Other studies reported higher incidence probably due to a different population case mix: the age-standardized incidence rate in women and men was 8.6 and 0.7 per 100,000 person-years, respectively. This rate was highest among black women (30.5), followed by Hispanic women (8.9), Asian women (7.2) (Dall'Era 2017). CLE includes three subsets of LE-specific skin diseases: - acute cutaneous lupus erythematosus (ACLE) - subacute cutaneous lupus erythematosus (SCLE) - chronic cutaneous lupus erythematosus (CCLE). CCLE encompasses discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LE tumidus), lupus profundus (also known as lupus panniculitis), chilblain lupus erythematosus (chilblain LE), and lichenoid cutaneous lupus erythematosus-lichen planus overlap syndrome (LE-LP overlap syndrome).  Source: Merola 2021 Although ACLE, SCLE, and the variants of CCLE are described as distinct entities, patients may develop more than one form of cutaneous LE. Many patients, up to 30 percent in some reports, may have overlap between subsets of cutaneous LE, particularly SCLE and DLE (Biazar 2013).

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 application regards the inclusion in the Model List of hydroxychloroquine for CLE with or without associated SLE. In 2011, the Expert Committee recommended the inclusion of hydroxychloroquine for SLE in the EMLc Complementary List with ophthalmologic monitoring as a condition for its use. The approach to the treatment of LE-specific skin disease is influenced by the subtype of disease and the presence of underlying SLE. First-line therapy typically involves photoprotection and topical or intralesional corticosteroids, topical calcineurin inhibitors. Systemic glucocorticoids can be used depending on the extent of involvement and subset of disease as well as systemic antimalarial agents. Topical corticosteroids are included in the Model List under dermatological medicine list (section 13). Second-line therapy typically involves glucocorticoid-sparing and immunomodulatory therapy and should take into account underlying SLE end-organ manifestations, if present. For instance, methotrexate (oral or subcutaneous) may provide additional benefits for SLE with inflammatory arthritis component. Mycophenolate mofetil may be of dual-benefit to patients with underlying lupus nephritis. Other second- or third-line agents may include: thalidomide, lenalidomide, systemic retinoids, oral dapsone, belimumab, or azathioprine. Hydroxychloroquine is widely recommended for all patients with CLE and SLE.
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 recent systematic review included five retrospective studies (329 patients), 3 prospective cohort studies (353 patients), two case series (37 patients), and two randomised controlled trials (RCTs, 133 patients) (Shipman 2020). One RCT including 58 participants compared hydroxychloroquine (400 mg/d) to acitretin, a vitamin A derivative, for 8 weeks (Ruzicka 1992). Hydroxychloroquine was slightly more effective than acitretin (50% vs 46%); however, the incidence of adverse event, mostly mucocutaneous symptoms, was much lower in hydroxychloroquine-treated patients (57% vs 96%). There were no reports of retinopathy during the study. A multicenter RCT conducted in Japan in 103 participants compared the sequence hydroxychloroquine and placebo given over a 16-week double-blind period, followed by a 36-week single blind period in which all patients were given hydroxychloroquine (Yokogawa 2017). The doses were 200 mg/d, 200 and 400 mg/d on alternate days, or 400 mg/d based on body weight. The primary outcome was CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index). CLASI scores at 16 weeks were significantly improved in both the HCQ and placebo but there was no difference between groups (-1.6, 95% CI -4.3 to 1.1, p=0.197). Secondary end point using photo evaluation and patient assessments favored hydroxychloroquine. Both groups continued to show decreasing CLASI scores after 32 weeks. Adverse events included cutaneous reactions, meningitis, and hepatic dysfunction No retinopathy occurred in either group. In a systematic review with meta-analysis cited in the Application, including both retrospective and prospective cohort studies and the two RCTs mentioned above, hydroxychloroquine (1284 courses of use among 16 studies) yielded an overall response rate of 61% (95% CI 50–71). The statistical heterogeneity was very high,

	limiting the reliability of this pooled estimate. According to an analysis of the European Society of Cutaneous Lupus Erythematosus (EUSCLE) antimalarials such as HCQ and CQ were used by 56.7% and 30.8% of the CLE patients, respectively, with an efficacy of 86.9% and 81.5%, respectively (Siggel 2013). Hydroxychloroquine was significantly more effective in ACLE patients than in CCLE (84.1%) or ICLE patients (77.4%) but the efficacy was not significantly higher compared to patients with SCLE (86.1%)
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).** Given that high-quality studies assessing the efficacy and safety of hydroxychloroquine for CLE are not available, it is difficult to assess the real benefit and magnitude of the effect associated with the use of hydroxychloroquine for CLE. At variance with what is stated in the Application, hydroxychloroquine did not demonstrate its superiority over placebo in the context of an RCT. Several cohort studies suggested a benefit using hydroxychloroquine in terms of response and amelioration of the disease. These data led to consolidate its use in CLE. Data on quality of life and psychological well-being are limited. **Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?** The Application does not report information on the efficacy hydroxychloroquine in diverse settings or population. The cutaneous manifestations of LE often result in depression and psychological stress. It is estimated that 20–40% of patients with cutaneous LE suffer from emotional problems, with studies including cohort of predominantly Black patients reporting higher prevalence (Hesselvig 2018, Hong 2019).
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Hydroxychloroquine is usually preferred over other antimalarials due to a better safety profile. Common adverse effects usually include digestive and cutaneous symptoms. Severe headache and dizziness, tinnitus and vertigo were also reported. Cardiotoxicity was rarely described in CLE patients but the lack of studies with adequate follow up may had precluded the possibility to detect these late events. The main safety issue related with the use of hydroxychloroquine is the increased risk of retinopathy. The overall prevalence was estimated up to 7% depending on dosage and duration of use. 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 (Melles 2014). The maximum daily dose advocated by the American Academy of Ophthalmology

	Guidelines is 5.0 mg/kg real body weight (Marmor 2016). The Application reports that severe late-onset toxicity including cardiotoxicity and myopathy seemed to have been rarely described in CLE patients. This Reviewer was not able to retrieve additional evidence on the issue of cardiotoxicity of hydroxychloroquine in this population. The literature indicates that antimalarial cardiotoxicity may be of particular importance in patients with SLE given their already increased cardiac risk due to primary heart disease and accelerated atherosclerosis. In a multinational, retrospective study assessing over 900,000 patients with rheumatoid arthritis aged 18 years or older initiating hydroxychloroquine no increased risk of severe adverse events was identified in the short term (30-days of administration). However, long-term use of hydroxychloroquine appeared to be associated with a small but significant increased cardiovascular mortality (Lane 2020).
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Retinopathy induced by hydroxychloroquine is not reversible, and there is no present therapy. Recognition at an early stage (before any retinal pigment epithelium loss) is important to prevent central visual loss. Several Ophthalmology Societies have issued guidelines for monitoring the risk of retinopathy in people taking hydroxychloroquine for any conditions. According to the American Academy of Ophthalmology Guidelines, a baseline fundus examination should be performed to rule out pre-existing maculopathy before starting the treatment. Annual screening after 5 years for patients on acceptable doses and without major risk factors is recommended (Marmor 2016).
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Given the limitation of the available evidence and the actual risk of retinopathy, the benefit harm profile of hydroxychloroquine for CLE with or without associated SLE appears uncertain. However, it should be noted that antimalarials are considered drugs of choice for CLE treatment since many years.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of evidence supporting this Application is low. Many of the studies were not RCTs, had small sample sizes, were limited in follow-up duration, and applied a retrospective design. Limited follow-up duration is important to consider, given that retinopathy and other AEs may take time to become detectable.

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: Monitoring of retinopathy (see above). The need for monitoring may create barriers to the use of hydroxychloroquine in disadvantage settings. The concomitant use of hydroxychloroquine and other medicines associated with cardiovascular side effects should be avoided. People with CLE and SLE should be advised to stop smoking because people with high smoking exposure significantly exhibited more severe skin issues or chronic damage.
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: Hydroxychloroquine is available in many countries, including UK, EU, USA, Canada, Australia and in low-income and middle-income countries.
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:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	No published cost effectiveness studies of hydroxychloroquine for the indication of CLE are available. However, affordability should not be an issue given the low prices of hydroxychloroquine. In Italy, Plaquenil 30 cpr 200 mg ex-factory price is 3.68 Euro. This means that 1 month of therapy costs from 7 to 10 Euros.
Any additional comments	The Expert Committee may wish to consider listing hydroxychloroquine also for SLE. Hydroxychloroquine is widely recommended for all patients with SLE, given its multiple beneficial effects (Ruiz-Irastorza 2010). As previously mentioned, concerns about retinal toxicity associated with long-term hydroxychloroquine calls for the use of daily doses below 5 mg/kg real body weight. It should be noted that most of the studies demonstrated the efficacy of a prescribed dose of 6.5 mg/kg/day, thus it remains to be confirmed whether a lower dose will have comparable clinical effects. Patients in long-standing remission may have their dose lowered, although no studies have formally addressed this strategy (Fanouriakis 2019).
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	This Reviewer is of the opinion that hydroxychloroquine may be recommended for the inclusion in the Model List for the systemic treatment of CLE, given its consolidated use worldwide. The recommendation should specify ophthalmologic monitoring as a condition for its use.

Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	
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