I.6	Methotrexate – psoriasis – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: This Application refers to the inclusion of methotrexate as an individual medicine for the treatment of severe psoriasis in children and adults. This Reviewer recognizes the global burden caused by psoriasis and the need for addressing this relevant public health need. The therapeutic approach to psoriasis includes topical treatments as a single strategy and a first-line therapy in the management of minor forms. The WHO Model list of Essential Medicines already includes several topical treatments for the treatment of psoriasis, such as vitamin D analogues (calcitriol, calcipotriol, tacalcitol), corticosteroid (betamethasone, hydrocortisone), and salicylic acid. Patient adherence may be a barrier to treatment success with topical therapies. Nevertheless, about 20% to 30% of people with psoriasis have a moderate-to-severe form requiring a second-line therapy, including phototherapy and non-biological systemic agents, such as ciclosporin, methotrexate, or acitretin. Methotrexate is a folic acid antagonist and one of the oldest oral pharmacological treatments licensed for psoriasis, together with ciclosporin and acitretin. It is already included on WHO Model Lists of Essential Medicines for the treatment of several oncological diseases, both solid and haematological malignancies, and the chronic inflammatory disease rheumatoid arthritis. Methotrexate has been used successfully in the treatment of psoriasis for over 50 years and it is also effective for the treatment of psoriatic arthritis and psoriatic nail disease. Although methotrexate appears to be less effective than biologic agents (at least some of them), it is still widely included in clinical guidelines and may represent a first choice of systemic agent in several countries. Methotrexate is the most common systemic medication used for moderate to severe pediatric psoriasis, despite the very limited evidence from clinical studies. Dermatologists select it mainly for its established use, long-term efficacy and safety data, weekly dosing, and possible efficacy on psoriatic arthritis. This Reviewer is in favour of adding methotrexate on the WHO Model Lists of Essential Medicines and Essential Medicines for Children. However, a comprehensive revision of treatments for moderate to severe psoriasis, including biologic agents, would better inform the selection of the most (cost-) effective agent(s), considering also safety and feasibility of administration across global settings. Please, see Application A_51 for further details.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Psoriasis is an immune-mediated disease with either skin or joints manifestations, or both. It is a chronic, non-communicable, painful, disfiguring and disabling disease with great negative impact on patients' quality of life (QoL). According to the 2016 WHO report on global impact of on psoriasis, the reported prevalence of psoriasis in countries ranges between 0.09% and 11.4%, making psoriasis a serious global problem. It is common in the age group 50–69, equally prevalent in both sexes, although some studies suggest that psoriasis is more common in men. Global average DALY for psoriasis for 2010 was estimated at 1 050 660, which is twice as much as for acute hepatitis C. It should be noted that data on prevalence and burden of psoriasis are extremely difficult to compare, due to differences in the definition of prevalence itself, case definition, population ages studied, sampling techniques. (https://www.who.int/publications/i/item/9789241565189). Psoriasis involves the skin and nails, but is also associated with several comorbidities. Between 1.3% and 34.7% of people with psoriasis develop chronic, inflammatory arthritis (psoriatic arthritis) that leads to joint deformations and disability. Numerous studies have reported the coexistence of psoriasis and other serious systemic diseases, most often mentioned are cardiovascular diseases, metabolic syndrome, including hypertension, dyslipidaemia, diabetes mellitus, and Crohn's disease. Psoriasis also causes great physical, emotional, and social burden: discrimination and stigma are often psychologically devastating for individuals suffering from psoriasis and their families. Various treatment strategies allow sustained control of disease signs and symptoms, but there is currently no definitive cure.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: According to the Application, overall published studies support the view that methotrexate used in the treatment of psoriasis results in a Psoriasis Area and Severity Index (PASI) 75 or significant recovery in about half those receiving the medicine (West et al., PLoS One 11(5): e0153740). A Cochrane review showed that the relative effects of methotrexate versus placebo, estimated from the network meta-analysis model, was 6.97 (95% CI 1.42 to 38.37) for PASI 90 (388 patients, 5 studies, moderate certainty of evidence). The results were similar for other efficacy outcomes, such as PASI 75 but they should be interpreted with caution given the limited number of studies (participants) in the network (Sbidian et al., Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD011535). Few randomized trials have compared the efficacy of cyclosporine and methotrexate, with varying treatment regimens and providing different results. No significant difference emerged. However, renal toxicity and hypertension are common with cyclosporine, thus limiting its long-term use and requiring close monitoring in people with psoriasis. Methotrexate appears to be less effective than biologic agents, that are however not accessible in several world regions (Sbidian et al., Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD011535). **Children and adolescents** The Application lacks sufficient details on studies involving children and adolescents. Small retrospective studies and registry based prospective cohort study (for instance Child-CAPTURE registry) suggested safety and efficacy of oral and/or subcutaneous methotrexate (Van Geel et al., J Dermatolog. Treat. 2015;26(5):406-12).

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The safety profile of methotrexate is well established considering its used in several conditions. Severe harms are very rare but when encountered are most often secondary to myelosuppression. Liver toxicity may require specific monitoring. According to the Cochrane review updated to 2022, the direct evidence reported that the risk of serious adverse events (SAEs) was significantly lower for participants on methotrexate compared to placebo (RR 0.16, 95% CI 0.03 to 0.88) and significantly higher for participants on infliximab compared to methotrexate (RR 2.41, 95% CI 1.04 to 5.59). When both direct and indirect evidence were assessed, the risk of SAEs was significantly lower for participants on methotrexate compared with all interventions, except bimekizumab, certolizumab, netakimab, deucravacitinib, and apremilast (Sbidian et al., Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD011535). **Children and adolescents** Methotrexate is considered safe in children based on its wide use in other diseases (rheumatology). An international, multicenter, retrospective study focused on the tolerability and observed AEs of systemic treatment in moderate to severe psoriasis in children (Bronckers et al., JAMA Dermatol. 2017;153(11):1147-115). Methotrexate was the most commonly used systemic treatment for moderate to severe psoriasis in children in both North America and Europe (about 70% of participants). The most frequently reported adverse effects of methotrexate were gastrointestinal (nausea and dyspepsia) and increase of transaminase, while injection site reactions and infections were more frequent with biologics.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Older patients and patients with decreased kidney function are at increased risk for hematologic toxicity and may require monitoring and dose adjustment. In general, evaluation of renal function with eGFR is recommended at baseline.

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Methotrexate is usually administered in an intermittent low-dose regimen, such as once weekly, as in patients with rheumatoid arthritis. Administration can be oral, intravenous, intramuscular, or subcutaneous. The concomitant administration of folic acid may protect against some of the common side effects seen with low-dose methotrexate, such as stomatitis and other gastrointestinal manifestations. However, to date, there are no consensus guidelines for dosage and timing of folic acid administration (Van Huizen et al, JAMA Dermatol. 2022;158(5):561-572). Absolute contraindications include pregnancy, nursing, alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes, bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia, or hypersensitivity to methotrexate. Relative contraindications include liver and renal function abnormalities and active infection.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: Methotrexate is considered among the most cost-effective systemic treatment for psoriasis in terms of the number of patients needed to treat to achieve a PASI 75.
Are there 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: Methotrexate is licensed in a broad range of countries for the treatment for psoriasis in adults. It is usually used outside of its normal licence in children and adolescent with inflammatory diseases.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: No WHO guidelines for the use of methotrexate in psoriasis.