I.6	Methotrexate – psoriasis – EML and EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: The body of evidence from a systematic review and network meta-analyses suggests that among the options for treating patients with moderate to severe psoriasis, methotrexate (MTX) is only better than placebo but inferior to most of the interventions at the same level of indication (i.e., patients who have poor response to topical therapies and UV therapy). Also, the evidence suggests that MTX is among the drugs most likely to be harmful. Since MTX is still cost-effective and cheaper when compared to newer options, it is possible to be recommended given that individual values from patients are incorporated in the decision-making process to address issues of balance of the benefits vs possible harms/undesirable effects.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Psoriasis is a chronic skin disease affecting roughly 2% of the population worldwide, although with some differences in the rates among regions (e.g., high rates in island populations and lower among native Americans). Incidence varies between 2.3 to 30 per 100,00 persons per year in different countries. It is estimated that at least 60 million people worldwide are affected. The mean age of onset for the first presentation of psoriasis ranges from 15 to 20 years of age, with a second peak occurring at 55–60 years. Psoriasis affects the quality of life of patients with stigmatisation, depression, and even suicidal thoughts. Co-morbidities include psoriatic arthritis, obesity, cardiovascular disease, and raised serum lipids, among others.
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: Methotrexate has long been considered first line of therapy in several guidelines for patients with moderate to severe psoriasis who fail to respond to initial topical therapies, and it is listed in the EML for psoriatic arthritis. Evidence from several RCTs comparing MTX to placebo and other comparators are assessed in a recent NMA from Cochrane. In this, for reaching PASI 90, MTX was superior only to placebo, but no difference of effects was observed when compared to other interventions of common use today, including non-biological medications (cyclosporine, acitretin, apremilast), biologic agents such as TNF inhibitors (adalimumab, certolizumab, etanercept) and IL inhibitors (ustekinumab, ixekizumab, guselkumab, tildrakizumab, secukinumab, risankizumab, and bimekizumab). MTX was only inferior to infliximab for PASI 90. Similar results were observed for the Physician Global Assessment (PGA) score. No difference in the HRQOL measures was observed with any of these interventions, except for placebo.

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 same body of evidence provides information on harms. In this case, the evidence suggests that MTX is among the medications with most probability of harms. As mentioned below, there are several AEs of special interest for decision makers; these are rare and include liver toxicity, bone marrow suppression, and pulmonary and renal effects; other common AEs include nausea and intercurrent infections which are manageable.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: There are several AEs of special interest for decision makers; these are rare and include liver toxicity, bone marrow suppression, and pulmonary and renal effects; other common AEs include nausea and intercurrent infections which are manageable.
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: Due to its profile of harms and toxicity, only experienced health professionals should prescribe and monitor the treatment with MTX in patients with moderate to severe psoriasis.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: MTX is considered the most cost-effective systemic treatment for psoriasis in terms of the number of patients needed to treat to achieve a PASI 75, according to a literature review in the Journal of the American Academy of Dermatology. Methotrexate (2.5-mg tablet) cost an adjusted $794-$1,503 a month per number needed to treat (NNT) for a 75% reduction in Psoriasis Area and Severity Index (PASI 75) score. However, no specific studies were available of current ICERs using methotrexate. The most recent data comes from a study in the Philippines where monotherapy with MTX will cost 4278 USD over 6 years per patient and the budget impact analysis over a 5-year time horizon will be of 2,232,324 USD, still cheaper than the closest option (secukinumab) at more than 35 million USD.
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: MTX has been in the market for long time, and it is already in the EML for other indications.

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 guidelines for the specific recommendation was found.