F.9	Methotrexate (sub-cutaneous injection)
Draft recommendation	☒ Recommended ☐ Not recommended Justification: The application regards the inclusion of methotrexate administered subcutaneously for the treatment of several conditions: • rheumatoid arthritis in adult patients • polyarthritic forms of juvenile idiopathic arthritis • psoriasis vulgaris and psoriatic arthritis • Crohn's disease These diseases are frequent and widespread in all geographic areas and methotrexate is one of the mainstays of treatment for these conditions. The WHO EML includes methotrexate for two indications: cytostatic agent in cancer treatments and immunomodulating agent (disease modifying) for (chronic) inflammatory diseases. Both oral and intravenous formulations are listed. Oral formulations may be suboptimal in severe cases and their pharmacokinetics appears to be variable with possible effects on clinical and safety outcomes. Errors with the dosing of methotrexate for treating inflammatory diseases have been reported, prompting the EMA to issue prescribing measures, such as restricting who can prescribe these medicines, packaging modification and warnings, providing educational materials for patients and healthcare professionals. Parenterally administered methotrexate results in rapid and almost complete absorption, higher serum levels, and less variable exposure than oral dosing. Intramuscular injection may increase the risk of infection. Data on clinical efficacy and safety of subcutaneous methotrexate compared to oral or intramuscular formulations are limited and, overall, do not fully clarify the possible benefit of subcutaneous methotrexate. No data on discontinuation/drug survival or compliance have been provided. However, bioavailability data suggest higher concentration following subcutaneous administration, but no substantial impact on response or side effects. It has been suggested that dose adjustments, but not necessarily the route of administration, increase efficacy, but some patients may benefit from switching to parenteral route. No cost effective data are reported by the Application, however access and affordability appears not to be an issue as generics are available in several countries (at least of the pre-filled syringe). This Reviewer acknowledges the lack of evidence on clinical superiority of subcutaneous formulation, but understands subcutaneous methotrexate may increase treatment options for those situations where oral formulations are not optimal. The Committee should consider including subcutaneous methotrexate on the WHO EML.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The application regards the inclusion of methotrexate administered subcutaneously for the treatment of several conditions: • rheumatoid arthritis in adult patients • polyarthritic forms of juvenile idiopathic arthritis • psoriasis vulgaris and psoriatic arthritis These conditions represent a significant public health concern. However, it should be noted that several treatments are available and already listed on the WHO EML, as well as oral and intravenous formulations of methotrexate. The inclusion of an additional formulation may increase treatment options but it does not have a high priority itself.

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: As stated in several parts of the application, there is limited evidence comparing oral methotrexate to subcutaneous methotrexate, and in most of the literature both dosing are used interchangeably. A mix of primary studies and narrative/systematic reviews were summarised by the Applicant. Most of the evidence regards people with rheumatoid arthritis. Very limited data is provided on other conditions, such as juvenile idiopathic arthritis and psoriatic disease. A 6-month prospective, randomized, controlled trial examined oral versus subcutaneous methotrexate on 384 methotrexate -naive patients with active rheumatoid arthritis (Braun et al ARTHRITIS & RHEUMATISM 2008;58, 73–81). At 24 weeks, the percentage of patients with an ACR20 and ACR70 response were higher in the group receiving subcutaneous methotrexate. No statistically significant difference for ACR50 was found. A 3-month randomised trial evaluated the efficacy and safety of subcutaneously administered methotrexate in 102 methotrexate-naive Japanese patients with active rheumatoid arthritis (Tanaka et al Modern Rheumatology 2022; 1-10). No statistically significant differences for ACR20 ACR50, and ACR70 were found compared to oral methotrexate. Other studies investigated bioavailability of the two formulations. One head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis showed that subcutaneous methotrexate bioavailability was higher than that of oral methotrexate across all tested doses (Schiff et al. Ann Rheum Dis. 2014;73(8):1549–1551, Hoekstra et al. The Journal of Rheumatology 2004; 31:4, Pichlmeier et al. Clinical and Experimental Rheumatology 2014; 32: 563-571). One study compared the relative bioavailability of low dose methotrexate administered as tablet, oral solution, and subcutaneous injection to that of intramuscular injection in 12 patients with rheumatoid arthritis. Data suggest that subcutaneous methotrexate may be an alternative to intravenous formulation (Jundt et al. J Rheumatol 1993;20(11):1845–1849). A post hoc analysis of the CAMERA study suggested that subcutaneous methotrexate may be useful as treatment step after oral methotrexate in a tight control strategy (Bakker et al. Ann Rheum Dis. 2010 Oct;69(10):1849-52) Overall, the certainty of evidence appears to be low.
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: Data on the harm profile for the subcutaneous methotrexate compared to oral formulations are scarce. Some studies reported a significant reduction in gastrointestinal side effects compared with equivalent oral administration No data on discontinuation/drug survival or compliance have been provided.

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
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: There are no special monitoring/requirement for the administration of subcutaneous formulation compared to the oral or intramuscular. Errors with the dosing of methotrexate for treating inflammatory diseases have been reported, prompting the EMA to issue prescribing measures, such as restricting who can prescribe these medicines, packaging modification and warnings, providing educational materials for patients and healthcare professionals.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: No data on comparative cost effectiveness over other formulations are reported in the Application. Generics are available in several countries, with variable costs.
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: Subcutaneous methotrexate is licensed in most high and middle income countries.
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: There is no WHO specific guideline for the conditions covered by the Application.