F.9	Methotrexate (sub-cutaneous injection)
Draft recommendation	☐ Recommended ☒ Not recommended Justification: The application focusses on the potential role for subcutaneous formulations of methotrexate. A wide range of potential formulations are included in the application. Very limited comparative RCT clinical efficacy or safety data is available between oral and SC MTX. There is very limited data in conditions other than Rheumatoid arthritis. Very limited data on cost-effectiveness is available. A range of formulations are available from multiple generic providers, but it is unclear which is the specific optimal dose and formulation to treat adults and children.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The application is for sub-cutaneous methotrexate for a range of inflammatory conditions, including RA, JIA, PSA and Crohn's disease. These are significant public health concerns as has been noted in other medicines listed on the EML.
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: Very limited data is available on the efficacy of SC MTX. I could identify one RCT comparing oral to SC MTX, with very limited patient information, where adults with RA had a slightly improved response at 24 weeks (78% vs 70% achieving a 20% improvement) (Braun 2007), with key trial information not available. Other smaller studies provide limited clinical information. A SR in 2016 (Goodman et al) confirmed the lack of comparative efficacy and toxicity data, noting that the absorbed dose appeared to be the key determinant of successful outcome rather than the route of administration. An open label study sponsored by Nordic Pharma (SELF-1 trial) compared the auto-injector to pre-filled syringes of MTX and identified similar clinical outcomes, but a patient preference for the auto-injector. Very limited data is provided on efficacy in non-RA conditions.
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: Very limited safety data on SC MTX is provided in the application, which summarises data on safety for all formulations of MTX. The small number of open label studies provide limited evidence on the safety of SC MTX. Bioequivalence of MTX appears to be improved with SC compared to oral MTX and higher doses are associated with GI symptoms.

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: The auto-injector appears to have only low levels of local infection site reactions.
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: No special monitoring is required for SC other than for all MTX therapy.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: No clear cost effectiveness data on SC MTX, compared to oral MTX is provided in the application. Multiple generic formulations of pre-filled pens and injectors are currently available in varying costs and doses.
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: A wide range of licensed formulations are available in many 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: