A.2	Anakinra – macrophage activation syndrome in systemic onset JIA
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☒ No ☐ Not applicable This application is for SOJIA with MAS JIA is 1.6-2.3 per 100,000: SOJIA is 4-9% of JIA: MAS is about 30% in SOJIA Reference citing prevalence in India (Reference 38) is not acceptable – It is an Editorial and modeled the prevalence from world wide data. Percentage of SOJIA given in this Editorial has cited two references: These Two limited (and not direct prevalence) studies done in 1996 and 2010 Reference 14 is a chapter in a Text book published in 2016 – I could not check it Children: Estimates for Asia and Africa have been derived from known prevalence rates of JIA and modelling using population data for each country
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.	Section 29 in EMLc and EMLa is Medicines for diseases of joints This is classified into 3: Gout, DMARDs, Medicines for Juvenile Joint diseases Gout: 1. Allopurinol for adults 2. EMLc- Section is deleted DMARDs: 1. CQ, HCQ, SSZ, Penicillamine, MTX and AZP in EMLa 2. HCQ and MTX in EMLc Juvenile Joint Diseases (include KD, Juvenile Arthritis and rheumatic fever) 1. List acetylsalicylic acid in both lists Do we need to review this section? We do not have JIA as a sub section in EMLc or EMLa (assuming JJDs imply JIA??) As per the application Current treatments of SOJIA include **steroids (oral or intravenous**) and **disease modifying anti-rheumatic agents (DMARDs), such as Methotrexate, Anakinra or Tocilizumab**. Methotrexate, whilst known to be efficacious in many forms of JIA, has a limited role to play in SOJIA when used as a sole therapy (21) but is often used in combination with a biologic DMARD such as Tocilizumab. **Reference 21** *(Boom V, Anton J, Lahdenne P, Quartier P, Ravelli A, Wulffraat NM, et al. Evidence based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2015;13:55)* It is for treatment of MAS in JIA (which is about 30% in JIA) MAS independent of JIA is also prevalent Results summary (abstract) **The highest level of evidence for treatment comes from retrospective case-series (evidence level 3).** High dose corticosteroids with or without cyclosporine A were frequently reported as first-line therapy. From the newer treatment modalities, promising responses have been reported with Anakinra.

	MAS in SOJIA is not in EMLa or EMLc • Steroids are not in EMLc or EMLa under this section • We have MTX in both EML and EMLc • I understand that an application has been made for Tocilizumab • Ciclosporin is also not in EMLa or EMLc This stresses the need for review of this section
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:
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). From the application: Due to the small numbers of trials, and small numbers of patients involved, the systematic reviews and meta-analyses review these same individual trials, however all these reviews outline in detail the difficulty of drawing clear conclusions due to variations in outcome measures and datasets. Application is for MAS in SOJIA 1. No RCTs 2. Two small studies (observational – in children) 3. Both are case series 4. One study is already included in Reference 21 (systematic review) 5. Other study - *Thirteen sJIA patients and two AIDs patients were included the study. Nineteen MAS episodes were observed in 15 patients. Anakinra (2 mg/kg/day) was started in with a median 1 day after admission. Clinical symptoms resolved, and laboratory findings normalized within median (minimum–maximum) 2 (1–4) and 6 (4–9) days, respectively after the introduction of anakinra. Steroid treatment was stopped in a median of 10 (4–13) weeks after the initiation of anakinra treatment. Patients were followed up for a median of 13 (6–24) months.* Inadequate evidence Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Not in elderly or pregnant patients.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☒ No ☐ Not applicable Comments: As for efficacy, very limited evidence

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: 1. The most serious side effects have included infections and neutropenia (1-10%), while the most common side effects have included injection site reactions (> 10%). 2. Tuberculosis
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Uncertain
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Low
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: MAS in SOJIA is a serious condition and treating any diseases with interleukin-1 inhibitors also needs specialized care
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: Not registered in many resource limited countries in Asia and Africa
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.	1. Not in the National EMLs of many countries (not in any of the NEMLs I checked) 2. Will not be affordable for RLCs (annual cost for a 10 kg child has been estimated as £67,017.65 3. WHO EML has not listed first line option (steroids) yet
Any additional comments	

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 Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	NOT RECOMMENDED REASONS: 1. Prevalence data are not reliable for many countries 2. Available prevalence data indicate MAS/SOJIA/JIA is rare 3. No RCTs examining the efficacy of this product in the given indication 4. No safety data (postmarking) from countries where it has been registered 5. So, Efficacy and safety are uncertain REVIEW OF THIS SECTION IS REQUIRED FOR EMLa AND EMLc
References (if required)	