A.2 (item number)	**Anakinra - Macrophage Activation Syndrome in SOJIA** (application title)
Does the application adequately address the issue of the public health need for the medicine?	■ Yes ☐ No ☐ Not applicable *Comments: Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of childhood, affecting approximately one per 1000 children. The proportion of children with JIA who have SOJIA ranges from approximately 10% to 50%. SOJIA can be complicated by the serious and often fatal Macrophage Activation Syndrome (MAS) in 33% of patients. The mortality rate is up to 23% in SOJIA.*
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.	*There are no other therapeutic agents currently included in the Model List, specifically for MAS/SOJIA. Acetylsalicylic acid* (acute or chronic use) is listed for juvenile joint disease in general:* • *21st WHO Model List of Essential Medicines (2019) - pg 5, 29.3 Juvenile joint diseases - acetylsalicylic acid* (acute or chronic use).* • *7th WHO Model List of Essential Medicines for Children (2019) - pg 37, 29.3 Juvenile joint diseases - acetylsalicylic acid* (acute or chronic use).* *Anakinra has not been recommended (EMA, FDA) for children with Juvenile Rheumatoid Arthritis in general. However, the use of anakinra was recommended as initial therapeutic option for patients with features concerning for MAS (level C rating evidence – from uncontrolled studies, including case series) by the American College of Rheumatology (2013 JIA Guideline).*
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 X ☐ 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). *All available evidence is based on small case series with no control group. Although some case series followed patients for an adequate period ((5 years) and reported disease-related outcomes (proportion of patients with inactive disease), the lack of control group prevents any conclusion on the efficacy/effectiveness of Anakinra for children with MAS/SOJIA.* Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? *No. There is no available evidence on low-resource settings. Most case series presented are from North America or European countries.*
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	■ Yes ☐ No ☐ Not applicable Comments: *There is almost no evidence of safety outcomes about Anakinra for MAS/SOJIA patients. The available case series usually presented a high number of non-serious and serious adverse events. Still, the very small number of patients prevents any solid conclusion on specific adverse events.*
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ■ No ☐ Not applicable Comments: *limited information about adverse effects.*
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	*The overall benefit to risk ratio is highly uncertain because of the lack of evidence both for efficacy/effectiveness and safety.*
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	*The overall quality/certainty of evidence is very low for relevant outcomes due to methodological limitations (non- comparative studies) and imprecision (small sample size/number of events).*

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:
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: *the recommendation of Anakinra for MAS/SOJIA is not present in the FDA and EMA official documents.* *The applicant stated that the medicine is approved in a list of countries, but it is not clear if it is specifically for MAS/SOJIA***.**
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: *no guideline for MAS was found.*
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	*There is limited data for comparative cost evaluation and cost-effectiveness of Anakinra.* *Anakinra seems a highly cost medication with heterogeneous price, accessibility and affordability in different countries.* *The applicant presented a raw cost estimate of an annual cost for a 50kg child in four different countries:* *UK: $67017.65- $134035.30 £* *Australia: $19345 - $38690 AUD* *Canada: $15001.5-$3003 CAD* *USA $52012.5-$104025 USD*
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.	*It is worthy of recognising that the low prevalence of SOJIA/MAS and its clinical complexity may difficult the prospection of high-quality evidence and that there are relatively few therapeutic options available for these patients.* *However, the high uncertain estimates of clinical benefits and the probable burden and unequal affordability and access to this medication in different settings prevents a favourable recommendation to include this intervention on the EML and EMLc.* *Therefore, the proposed recommendation to the Expert Committee is to not* ***incorporate anankira on the EML and EMLc.***

References (if required)	*Ringold S, Weiss PF, Beukelman T, Dewitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA, Robinson AB, Vehe RK; American College of Rheumatology. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Care Res (Hoboken). 2013 Oct;65(10):1551-63. doi: 10.1002/acr.22087. PMID: 24078300; PMCID: PMC5408573.*