A.3	Anakinra – systemic onset juvenile idiopathic arthritis with macrophage activation syndrome – EML and EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: Prevalence of MAS in SOJA is very rare and data are not reliable for many countries and no randomized clinical trial with Anakinra are available for this indication. Also safety data are lacking, the high risk of infection like TB should be evaluated in a clinical trial before recommending this medication in countries with less resources and high prevalence of TB. We should also consider that the use of this medicinal product requires continuous and professional monitoring and follow-up care, training of nursing staff, and proper storage conditions. Anakinra must be administered daily as a subcutaneous injection, which can be a problem in less-resourced countries. I do not support the inclusion of Anakinra on the EML and EMLc for treatment of systemic onset juvenile idiopathic arthritis with macrophage activation syndrome at this time. Alternatives exist, like high dose corticosteroids (with or without cyclosporine A) are reported as first-line therapy.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: This specific application is for SOJIA complicated with MAS. Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, affecting approximately 1 in 1,000 children. The percentage of children with JIA who have SOJIA ranges from about 10% to 15%. SOJIA can be complicated by severe and often fatal macrophage activation syndrome (MAS) in around 30% of patients. SOJIA has a high mortality rate (up to 23%).

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: No RCT are available for application indication (MAS in SOJIA), only 2 small observational studies (cases series) in children are published: 1. A Turkish study evaluated the use of Anakinra to treat MAS in 15 paediatric patients, 13 with SOJIA and two had other autoinflammatory diseases. Nineteen MAS episodes were observed in these 15 patients. Anakinra (2 mg/kg/day) was started within a median of 1 day after admission. Clinical symptoms resolved, and laboratory findings normalized within median (minimum–maximum) of 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. Patients were followed up for a median of 13 (6–24) months. Two patients developed recurrent MAS episodes when the Anakinra dose was reduced, while the other patients achieved remission. No adverse events were noted. 2. A study from Canada reported on 12 children with MAS (8 due to SOJIA) who were refractory to Steroids, Cyclosporin A and IVIG. Five patients required intensive care. All patients achieved MAS remission after addition of Anakinra within a median of 13 (range 2–19) days. Corticosteroids were discontinued by 6 weeks in seven patients. Patients were followed for a median of 22 (range 2–40) months, and all were in remission of MAS at the final follow-up with excellent control of the underlying rheumatic disease. There were no reported side effects from Anakinra administration. In conclusion the lack of control group prevents any conclusion on the efficacy/effectiveness of Anakinra for children with MAS/SOJIA. There is no available evidence on low-resource settings. Most case series presented are from North America or European countries
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: 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: No enough data

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: As well explained in the application, the use of this medicinal product requires continuous and professional monitoring and follow-up care, training of nursing staff, and proper storage conditions. Anakinra must be administered daily as a subcutaneous injection, which can be distressing for both the child and caregiver. Who will administer the drug? Storage?
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: The applicant presented a cost estimate of an annual cost for a 50 kg child in four different countries (UK, Canada, USA, Australia): 10'000-100'000USD. Cost is high and there is absence of comparative cost or cost-effectiveness studies.
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: Anakinra's recommendations for MAS/SOJIA are not included in official FDA and EMA documents. Applicant has indicated that the drug is approved on the national list, but it is not clear if indicated to MAS/SOJIA.
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: