A.3	Anakinra – systemic onset juvenile idiopathic arthritis with macrophage activation syndrome – EML and EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: The application proposes use of anakinra for systemic onset juvenile idiopathic arthritis with macrophage activation syndrome. This condition has varied epidemiological importance worldwide, which reflects different incidence due to racial or ethnic disparities. Different sources suggest incidence varying from 5 to 115 cases per 100.000 to 3.8 to 400 per 100.000. Only 5 reported studies focusing on efficacy/effectiveness for SOJIA (150 patients) and 2 for SOJIA with MAS (27 patients), and one on safety, but for CAPS (another disease) (43 patients) were brought forth. Although there is some evidence of efficacy and effectiveness, with improved outcomes and quality of life, the studies that subsidize this intervention are few and samples are small, and available information comes from well-resourced countries only. Safety profile in the very brief evidence information shows the occurrence of AEs during therapy, with the possibility of serious AEs, such as infections and, specifically TB. Moreover, use of this medicine requires continuous and specialized monitoring and follow-up, training of caregivers and adequate storage conditions. Anakinra must be given daily as a subcutaneous injection, which may be a burden for children and caregivers alike. This medicine is only market-approved in countries in Europe and North America and in Australia and Israel, all with high-income economies. Cost is high and there is absence of comparative cost or cost-effectiveness studies. There are no protocols/guidelines for SOJIA with MAS. Given the lack of adequate evidence for efficacy/effectiveness or for safety of this medicine, and the justifications above, that elicit the difficulties in administration and care across resource limited settings, risks of AEs, restrictions in availability and imprecision as to incidence of indication, surmounted by high costs and absence of cost-effectiveness studies, I do not recommend the medicine in the proposed indication to substantiate an addition to the WHO EMLc and EML.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: According to the application, the proposed indication if for the treatment of Systemic Onset Juvenile Idiopathic Arthritis (SOJIA) with Macrophage Activation Syndrome (MAS) – SOJIA with MAS. Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of childhood and is the chosen name for a heterogenous group of autoinflammatory diseases characterized by the presence of chronic arthritis for more than 6 weeks and starting before 16 years of age. Aetiology in unknown, probably multifactorial. Pathological process is chronic inflammation and innate and adaptive immune systems interact[1]. The Systemic Onset JIA subtype (SOJIA) is characterised by arthritis, fever, rash and systemic inflammation and is now recognised as an autoinflammatory syndrome. MAS, a complication, is serious and may be fatal. Criteria for diagnosis of both have been validated. Early introduction of more aggressive therapy with anti-rheumatic disease modifying agents has been proposed as safe and effective, to avoid joint destruction, control the disease, improve quality of life and minimise long-term corticosteroid use. Epidemiologic studies carried out in less-resourced countries shows worse quality of life for children with SOJIA than that in well-resourced countries and detrimental social and economic implications for caregivers due to absences form work. Global prevalence of JIA has been estimated to range from 3.8 to 400/100,000 with an incidence of 1.6 to 23/100,000[2]. However, the proportion of those with JIA who have SOJIA is 10-15%, and 33% of those may present with MAS, which would give an exceedingly rough estimate of around 5 to 115 cases per 100.000. The varying incidence may reflect differences in racial or ethnic groups. This may burden some countries with higher incidence (mainly in Asia and Africa), while presenting a very small incidence rate in others.
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: The studies that subsidize this intervention are few and samples are small. There is some evidence of efficacy and effectiveness, with improved outcomes and quality of life, but in few studies for SOJIA (5 studies with a total of 150 patients) and even less for the special cases of episodes of MAS in SOJIA (2 studies, with 27 patients in both). The application admits that there are few studies. The few trials are in well-resourced countries, where standard of care involves a great deal of monitoring and follow-up.

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: Safety evidence is traditionally known to come out later than efficacy or even effectiveness, as larger numbers of an exposed population are needed for detection of adverse effects which have not been seen in research environments. In this case, there is admittedly no quantification of exposure to the medicine, because it may be used for other conditions. Also, there are no direct safety reports on MAS other than in the few descriptions that integrate cited studies. The only reported study with 5-yr follow-up of 43 patients to evaluate safety, but for the use of anakinra in another autoinflammatory condition Cryopyrin Associated Periodic Fever Syndrome (CAPS) found the medicine well-tolerated. Safety profile is deemed similar in adults and children. There are mentions of some side-effects in the efficacy studies, such as headaches and arthralgia (but which could be associated to the disease) and injection-site pain and swelling. These AEs were reported by AE reports, laboratory assessments, vital signs and diary reports. A total of 1233 AEs were reported during the study, with a yearly rate of 7.7 AEs per patient. According to the study AE rate decreased over time, and dose escalation during the study did not affect AE frequency. The overall risk profiles for IL-1 inhibitors (such as anakinra, canakinumab, and rilonacept) involve GIT disturbance, abnormal liver functions, hyperlipidaemia and Infections.[1].
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: As with several immunosuppressive therapies, there is underlying risk of infection, and there are reports of bacterial infections pneumonia and gastroenteritis, EBV and hepatitis. In the study that reported anakinra use in CAPS, of 43 patients 14 patients experienced 24 serious AEs. Another earlier source also denoted serious AEs (infections, vertebral collapse, and Crohn´s disease diagnosis), with 33.3% of discontinuation of therapy associated to AEs[3]. Moreover, there must be monitoring of tuberculosis risk in patients treated with this medicine, particularly in low-resource settings with high TB rates (consensus statements on JIA care in low resource settings present this as level 3b evidence, strength A statement with 100% consensus). JIA patients should also undergo TB prophylaxis when a positive PPD or Quantiferon test is issued at start of biologic therapy or if there is a conversion to positive TB status during therapy. The use of this medicines requires very special monitoring and follow-up, with several laboratory tests involved.

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: This is a big challenge for the use of this medicine, as it requires extensive monitoring and follow-up, for effectiveness as well as for safety. The medicine requires cold storage (2-8° C), and the need to train parents and caregivers, in relation to the administration and storage of the medication at home, as well as regular clinical monitoring, blood tests and assessments. Anakinra requires daily subcutaneous injection, which can be an additional burden to children and caregivers. Continuous clinical assessment involves monitoring systemic features such as rash or fever, joint inflammation, or systemic inflammation elsewhere (such as pericarditis), regular blood tests such as C-reactive Protein and Full blood Counts as well as markers of MAS (Ferritin, Triglycerides and Lipids, Liver Function Tests and Clotting Profiles), concomitant infections (such as TB, etc). Most studies have been done in well-resourced countries and there is practically no information on how children in treatment in low resource income countries would fare, comparatively, in absence of required treatment support. Many children in these scenarios are likely to have no access to specialist care.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Cost is relevant and there are no comparative cost studies to inform use of anakinra in the context of SOJIA MAS, much less cost-effectiveness studies. In the UK, estimated annual cost per 10kg child ranges from £9573.95 to 19147.90 (more than tocilizumab and less than canakinumab) and per 50kg child £9573.95 – 38 295.80 (less than both). Costs in different countries vary.
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 is registered in the following countries Australia, Canada, USA, Israel, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain, Sweden, United Kingdom, Iceland, Norway. Most are high-income well-resourced countries. Moreover, this medicine is registered for SOJIA and not for MAS, which would make indication for MAS off label even in these 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: No WHO Guidelines are available.

Additional references

1. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol Online J. 2021 Aug 23;19(1):135. doi: 10.1186/s12969-021-00629-8.
2. Al-Mayouf SM, Al Mutairi M, Bouayed K, Habjoka S, Hadef D, Lotfy HM, Scott C, Sharif EM, Tahoun N. Epidemiology and demographics of juvenile idiopathic arthritis in Africa and Middle East. Pediatr Rheumatol Online J. 2021 Dec 2;19(1):166. doi: 10.1186/s12969-021-00650-x
3. Quartier PAF, Cimaz R, Pillet P, Messiaen C, Bardin C, Bossuyt X, Boutten A, Bienvenu J, Duquesne A, Richer O, Chaussabel D, Mogenet A, Banchereau J, Treluyer JM, Landais P, Pascual V. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011; 70:747-54.