A.48	Tocilizumab – systemic onset juvenile idiopathic arthritis – EML and EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: JIA is an autoimmune, non-infectious inflammatory joint disease whose etiology is poorly understood due to genetic and environmental contributions. It differs from rheumatoid arthritis in clinical manifestations, prognosis, course of disease, and treatment approaches. The age of onset of JIA is generally young, with peak onset between one and three years, but persisting into adulthood in about 50% of cases. Systemic JIA (SOJIA) subtype - characterized by arthritis, fever, rash and generalized Inflammation - SOJIA requires special attention as it is different from other JIA subtypes. It is recognized as an autoinflammatory syndrome. The proportion of JIA children with SOJIA ranges from approximately 10% to 20% depending on the population, with higher rates reported in low-resource areas such as India. SOJIA can be complicated by a severe and often fatal macrophage activation syndrome (MAS) with an uncontrolled 'cytokine storm' with a mortality rate of up to 23% in SOJIA. Early detection and treatment of SOJIA is essential to improve outcomes and reduce the risk of MAS. I do not support the inclusion of Tocilizumab on the EML and EMLc for treatment of systemic onset juvenile idiopathic arthritis at this time. Only a small number of clinical studies have provided comparative evidence of efficacy/efficacy and safety. Furthermore, the quality of evidence in these studies was rated as low or very low. In terms of comparative effectiveness/efficacy and safety, there was no conclusive, high-quality evidence demonstrating differences between biologics in JIA (and less so in SOJIA). I have also two major concerns. First, disease surveillance and treatment with tocilizumab requires appropriate access to specialized care, family/caregiver training, and continued use of laboratory tests and evaluations. Access to appropriate care, treatment monitoring, and follow-up care may not be available in low-resource settings. My second concern is related to safety profile which includes a range of AEs and primarily infections, with respiratory infections being more common. Tuberculosis risk should be monitored in patients treated with this drug, especially in resource-poor settings with high tuberculosis rates. No studies published were performed in less-resourced settings.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The incidence of JIA is 1.6-23 per 100,000; the range of incidence may reflect true differences across different racial and ethnic groups but may also reflect ascertainment and selection bias in the clinical studies (36). SOJIA is the rarest subtype of JIA, accounting for approximately 4-9% of cases in European nations. However, it is more common in certain ethnic groups, representing up to 25% and 50% of JIA in India and Japan; this corresponds to 312,000 patients with SOJIA in India alone. SOJIA is typically a chronic illness affecting young children - the age of onset is typically 1-5 years - with significant burden of disease as patients usually require treatment for months to years after the onset of symptoms, as well as close monitoring for complications or flares of disease including the potentially fatal MAS.

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: Only a small number of clinical studies have provided comparative evidence of efficacy/efficacy and safety. Furthermore, the quality of evidence in these studies was rated as low or very low. In terms of comparative effectiveness/efficacy and safety, there was no conclusive, high-quality evidence demonstrating differences between biologics in JIA (and less so in SOJIA). Yokota et al reported a randomised, double-blind, placebo-controlled, withdrawal phase III trial for 56 Japanese children aged 2-19 years refractory to DMARDs and biologics. In the initial phase, ACR Pedi 30, 50, 70 responses were achieved by 51 (91%), 48 (86%), 38 (68%) of patients respectively. By week 48 of the open-label extension phase, ACR Pedi 30, 50, 70 responses were achieved by 47 (98%), 45 (94%), 43 (90%) of 48 patients. Besides, patients who remained on Tocilizumab in the double-blind phase had sustained improvement in clinical measures of effectiveness and wellbeing, whereas most of those in the placebo group (18/23 patients) needed rescue treatment. This is Category 1B evidence. Patients on Tocilizumab reported a decreased in mean corticosteroid dosage from 0.9mg/kg/day at enrolment to 0.2mg/kg/day at 52 week. 12.3% (19 patients) discontinued steroids. Yokota et al also evaluated the safety and effectiveness of tocilizumab (TCZ) in patients with systemic juvenile idiopathic arthritis (sJIA) in real-world clinical settings in Japan. Fever and rash symptoms improved from baseline to week 52 (54.6% to 5.6% and 43.0% to 5.6%, respectively). At 4 weeks, 8 weeks and 52 weeks, 90.5%, 96.2% and 99.0% of patients achieved normal C reactive protein levels (<0.3 mg/dL), respectively. Only one Randomized clinical trial is available comparing tocilizumab x placebo for SOJIA: De Benedetti et al described a randomised placebo controlled trial for 112 Italian children (age 2-17, persistent disease for >6 months and inadequate response to NSAIDs and glucocorticoids) of intravenous Tocilizumab. After 12 weeks, the primary end point of ACR Pedi 30 response and absence of fever was met by 85% (64/75) in the treatment group and 24% (9/37) in the placebo group $p < 0.001$. At week 52, 80% in the Tocilizumab group had at least 70% improvement, 48% had no active arthritis and 52% had ceased oral glucocorticoids. In this study, 84% of patients in the treatment group had previously been treated with a biologic agent, including 55% with and interleukin-1 inhibitor and 73% with an anti-TNF agent. A German registry study reported that over a 5-year period, 46 of 200 patients with SOJIA were treated with Tocilizumab. A clinical response rate (defined as no symptoms and normal inflammatory markers) of 35% was reported in the first 12 weeks of treatment, and inactive disease/remission on medication (as defined in the Wallace criteria (21)) was reported in 75% after 1 year. A trial comparing clinical outcomes and patient satisfaction with switching from intravenous to subcutaneous formulation for SOJIA and polyarticular JIA revealed no difference in active joint counts, physician or patient VAS and JADAS71, and 8/9 patients were satisfied with subcutaneous administration in terms of life quality, school success, and reduced school absenteeism. A study is currently ongoing to compare clinical effectiveness and safety of the four consensus treatment plans published by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) which include the biologic DMARDS: (1) glucocorticoids alone, (2) methotrexate, (3) interleukin-1 blockade, and (4) interleukin-6 blockade. Patients consenting to participation in the CARRA Registry are started on one of four Consensus Treatment Plans at the discretion of the treating physician. The outcome of primary interest is clinically inactive disease off glucocorticoids at 9 months, comparing non-biologic (Consensus Treatment Plans 1 + 2) versus biologic (Consensus Treatment Plans 3 + 4) strategies. Bayesian analytic methods will be employed to evaluate response rates, using propensity scoring to balance treatment groups for potential confounding. The results of this study will be important for a future submission. Evidence of efficacy for tocilizumab to date is based on clinical data from well-resourced centers. Therefore, in most resource-rich countries, tocilizumab is the recommended treatment for her children with SOJIA.

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: Overall, safety and side effect data are limited due to lack of data. In the only RCT from De Benedetti 2012 et al, they estimate the occurrence of serious adverse events of 25 events/100 patients year. In the observational study by Yokota et al (Yokota 2016), they reported higher incidence of serious adverse events of 54.5 per 100 patient years.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: The safety profile includes a range of AEs and primarily infections, with respiratory infections being more common. Tuberculosis risk should be monitored in patients treated with this drug, especially in resource-poor settings with high tuberculosis rates. No studies published were performed in less-resourced settings.
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: Disease surveillance and treatment with tocilizumab requires appropriate access to specialized care, family/caregiver training, and continued use of laboratory tests and evaluations. Access to appropriate care, treatment monitoring, and follow-up care may not be available in low-resource settings Tocilizumab is available as both an intravenous infusion and a subcutaneous injection. The subcutaneous injection offers significant benefits in the ease of availability for patients and their families and decreased associated costs (such as day case admission for infusion, staffing requirements). Dosing of subcutaneous Tocilizumab for SOJIA is based on a child's weight as follows: • Child <30kg: 162mg SC every 2 weeks • Child >30kg: 162mg SC weekly Intravenous Tocilizumab: • Child <30kg: 12mg/kg every 2 weeks • Child >30kg: 8mg/kg every 2 weeks Patients (and their parents) who are commencing subcutaneous Tocilizumab require education on the administration of the medication at home, as well as regular monitoring blood tests. The availability of a subcutaneous preparation has alleviated some of the barriers to care associated with infusions.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Overall, tocilizumab appears to be an expensive drug that varies in price, availability, and affordability in different countries. Cost is high, for SC and for IV dosage forms and yearly expenses may be around 12,000 pounds sterling.
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:
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: