A.48	Tocilizumab – systemic onset juvenile idiopathic arthritis – EML and EMLc
Draft recommendation	☐ Recommended ☒ Not recommended Justification: The application proposes use of tocilizumab for systemic onset juvenile idiopathic arthritis. This condition has varied epidemiological importance worldwide. JIA is reported as affecting 1.6-23/1000 children. However, the proportion of those with JIA who have SOJIA is 10-15%. Other sources place the proportion between 10 and 20%[1]. Epidemiologic studies carried out in less-resourced countries show worse quality of life for children with SOJIA than for those in well-resourced countries and detrimental social and economic implications for caregivers due to absences form work. But most of these studies have been done in high-income settings and access to adequate care and treatment monitoring and follow-up may not be available in less-resourced settings. Monitoring of disease and treatment with tocilizumab oblige adequate access to specialized health care, training of family /caregivers and a continuous availability of laboratory tests and clinical assessments. Not only treatment availability but monitoring and follow-up are tantamount for better outcomes. There are few studies with small numbers of patients that have produced comparative efficacy/effectiveness and safety evidence. Moreover, in addition to this, evidence quality is deemed low to very low. There is one RS&MA that has confirmed this. In terms of comparative efficacy/effectiveness and safety, there has been no conclusive good-quality evidence to demonstrate differences between biologics in JIA (and less so for SOJIA). Safety profile involves different AEs and mainly infections, being respiratory infections more frequent. There must be monitoring of tuberculosis risk in patients treated with this medicine, particularly in low-resource settings with high TB rates. Tocilizumab is market-approved in countries in Europe, North America and in Australia; demand has risen recently, because of its approval to treat Covid-19 in Europe and the USA. Cost is high, for SC and for IV dosage forms and yearly expenses may be around 12,000 pounds sterling. However, stronger economies with a broader cost-effectiveness threshold may find the medicines cost-effective compared to other treatments for SOJIA. Given the lack of adequate evidence for efficacy/effectiveness or for safety of this medicine in SOJIA, and the justifications above, that elicit the difficulties in administration and care across resource limited settings and risks of AEs, I do not recommend the medicine to substantiate an addition to the WHO EMLc or to 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). 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[2]. It is a different disease form rheumatoid arthritis in clinical presentations, prognosis, outcomes and treatment schemes. The onset is at an early age, usually 1-3 years of age, and in 50% the disease persists into adulthood. Uveitis is also a serious complication of JIA. 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, aiming at better physical and psychosocial function. Epidemiologic studies carried out in less-resourced countries shows worse quality of life for children with SOJIA than for those 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[3]. However, the proportion of those with JIA who have SOJIA is 10-15%. Other sources place the proportion between 10 and 20%[3]. Tocilizumab is available for adults and children as intravenous infusion, in different strengths – 80mg, 200mg and 400mg) and as a subcutaneous injection (162mg). Most epidemiologic studies have been done in high-income settings and access to adequate care and treatment monitoring and follow-up may not be available in less-resourced settings. In a study conducted in a low-resource setting, maintenance of biologic drug was not possible after 2 months, due to cost. Children with JIA in less-resourced countries are at risk for higher rates of active disease, joint damage and worse outcomes, compared to children in high-income countries. However, not only treatment availability, but monitoring and follow-up are tantamount for better outcomes.

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: Tocilizumab is an IL-6 receptor antagonist, employed in treatment of SOJIA in children aged 2 years or older, refractory to conventional treatment[2]. Two small studies form Japan portrayed better radiological outcomes and better bone formation with tocilizumab treatment. 'Catch-up' linear growth, which was associated to less corticosteroid exposure, was seen by a trial involving 83 patients. The other cited studies involved trials, 1 observational cohort, one phase IV follow-up, two observational registry studies, one open-label phase II trial and one SR&MA (Tarp et al, 2016). The trials, the observational cohort and the registry data pointed out that treatment with tocilizumab improved outcomes. Trials were based on the ACR Pedi 30 (defined as "at least a 30 % improvement from baseline in three of six variables, with no more than one remaining variable worsening by >30 %"), and registry data on a clinical response endpoint (defined as no symptoms and normal inflammatory markers). In these studies various positive results (such as absence of fever, absence of active disease, decrease of corticosteroid dosage) ranged from 48 to 91% in the patient samples. The SR&MA was conducted to compare tocilizumab, with canakinumab and rilonacept (IL-1 inhibitors). This study included 5 RCT and no significant differences between anakinra, canakinumab and tocilizumab were found for ACR30 outcomes. Some small differences, with superiority of tocilizumab and canakinumab over rilonacept were detected but evidence was of low quality due to study design. Indirect comparisons, with the disease as the object of analysis, such as the meta-analysis on the benefit-risk balance for biological DMARD agents in JIA (1458 patients, 19 RCTs) showed that those with SOJIA (treated with agents rilonacept, canakinumab or tocilizumab), had higher rates of therapeutic success without serious adverse events, when compared to patients with non-systemic JIA patients (not treated by these agents). Etanercept and adalimumab, already in the WHO EML, are anti-TNF alpha agents used in JIA, but not in SOJIA. A patient registry study (Horneff et al, 2017) showed favourable results for tocilizumab compared with etanercept in JIA. However, there are overall very few studies for tocilizumab in SOJIA and evidence of comparative effectiveness is inconclusive, due to small number of studies and patients involved. Moreover, quality of evidence of comparative effectiveness (trials, observational cohort) was considered to be of low to very low quality.

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: The previously mentioned trials and the registry studies showed some evidence of safety/harms, however better-quality evidence is lacking. In one trial (de Benedetti et al, 2012), there were 60 cases of infection in the tocilizimab group, 2 of which were serious, compared to 15 in the placebo group during the double-blind phase. During double-blind and extension phases there were 39 AEs, including 18 serious infections. Tocilizumab was discontinued in 6 patients because of altered aminotransferase levels. There were three cases of MAS. In a real-world setting, a 52-wk trial reported overall AEs (224.3/100 patient years) and serious AEs (54.5 PY), including infections and infestations. Tocilizumab was discontinued in 4.1% of patients. There were 2 deaths related to AEs and 7 episodes of MAS. In an observational registry study AEs were observed in 24% of patients and serious AEs in 4%, including Hodgkin´s lymphoma and gut perforation. Another observational study showed rates of adverse events higher in patients treated with tocilizumab compared to etanercept. (Risk ratio (RR) 5.3/patient year; p<0.0001). Serious AEs were more frequent with tocilizumab than with etanercept (Horneff et al, 2017). In a SR&MA tocilizumab presented slightly greater risk of AEs compared to canakinumab (OR = 0,25, IC 95% = [0,09 –0,71]). However, in terms of comparative safety, there has been no conclusive good-quality evidence to demonstrate differences between biologics in JIA (and less so for SOJIA).
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Infections, especially in the respiratory tract are the most common AEs in patients treated with tocilizumab, and associated risk should be monitored. Upper respiratory tract infections are present in mor than 10% of patients[2]. Also worthy of mention are varicella, herpes zoster, neutropenia and elevation of aminotransferases[2]. 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. Potential laboratory abnormalities, being the most frequent altered liver function, neutropenia and elevated cholesterol levels should be constantly monitored. And more comparative studies are needed focusing on comparative risk/benefit ratios of biological agents to treat JIA and SOJIA[4].

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: SOJIA has a highly variable course, but most patients will have e chronic course, with or without systemic symptoms. There is risk of development of potentially fatal Macrophage Activation Syndrome (MAS) mainly in low- income countries. Disease activity is monitored with standard assessment tools, among them the Juvenile Arthritis Disease Activity Score (JADAS), which includes Active Joint Count, Patient/Parent Visual Analogue Scale (VAS) and a Physician/health care provider VAS for disease activity, and blood markers of inflammation (such as CRP and ESR). Subcutaneous and intravenous dosing of tocilizumab is administered every week or every other week, based on child´s weight. Infusion reactions are not uncommon, especially for new and younger patients, and some may require pre-medication with intravenous hydrocortisone or an antihistamine. While infusions must be done in a specialized in-patient/day-care facility, subcutaneous injection can be done at home, but requires adequate training for administration and blood monitoring. For tocilizumab monitoring the following exams should be carried out: Blood counts (every 4 to 8 weeks in the first 6 months and after that every 12 weeks), AST/TGO and ALT/TGP (every 8 weeks in the first 6 months and after every 12 weeks), total cholesterol and fractions, and triglycerides (every 8 weeks in the beginning of treatment and afterwards every 6 months)[4]. Abnormal results will oblige dose tapering to cessation of use, depending on range and seriousness of AEs. However, interruption of medication is associated with high degree of disease recurrence. In respect to uveitis in JIA, after interruption of treatment with DMARDs, the patient must be monitored every 2 months, for 6 months and after this period be trained as to self-monitoring of sight, each eye separately, once a week, or keep screening at the treatment centre, if unable to self-monitor. An annual eye check-up is recommended[5]. Disease monitoring, as well as treatment monitoring obliges access to specialist paediatric rheumatologists and multi-disciplinary teams, frequently unavailable in less-resourced countries.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?

☒ Yes

☐ No

☐ Not applicable

Comments:

Basically, costs vary between countries and some jurisdictions are governed by patient access schemes with discounts which are kept confidential by the manufacturer.

Country	**Cost IV**	**Cost SC**	**C-E**	**Benefit scheme**
UK	£102.40 for 80mg vial, £256.00 for a 200mgvial and £512.00 for a 400mg vial	£228.28 for 162mg/0.9ml prefilled pen/syringes	ICER for tocilizumab for JIA (polyarticular subtype) as £38,656 per QALY gained	Manufacturer (Confidential)
	Annual cost 10kg child - £5935.28 Annual cost 50kg child -£11,870.56			
Australia	$82 for 80mg/4mL vial, $203 for 200mg/10mL vial and $405 for 400mg/20mL vial	---	---	Government subsidy ($6.60 -$41 per infusion) Manufacturer (Confidential)
Canada	$7000 to $13000 per year depending on BW and administration costs		Incremental cost-utility ratio (ICUR) of $69,787 (CD) per additional QALY compared to placebo with Methotrexate	---
Finland	---	---	Considered cost-effective: €15181 based on acceptability frontiers of 20,000euros/QALY gained	---
Thailand	---	---	ICER of standard treatment plus Tocilizumab was US $35799 per QALY (ST in Thailand involves NSAIDs, systemic CCO and non biologic DMARDs)	---
Russia	Cost of Tocilizumab is justified by better cost efficiency, reduced social and economic losses in the state budget. Annual budget losses due to the social burden of disease were substantially lower (226729.10 vs 426144.63RUB)			---

Depending on the established cost-effectiveness threshold in different jurisdiction, tocilizumab may or not be considered cost-effective. However, comparisons between biologic DMARDs are lacking, mainly RCTs for JIA subtypes[6].

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: The medicine is market-approved for the treatment of SOJIA in several countries and regions, notably Australia, North America, the UK and the European Union. Subcutaneous injections are approved for younger patients (1yr and older, with at least 10kg) and intravenous for older (2 yrs and older). Registration is not universal. Recently the FDA and EMA approved tocilizumab for the treatment of Covid-19, which may indicate that approval in other jurisdictions may be accelerated. Other consequences that may happen with greater demand are shortages. Recent reports of supply issues have arisen in India.
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

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