A.36 (item number)	Tocilizumab - Systemic onset juvenile idiopathic arthritis (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%. 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 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).* *Tocilizumab is recommended for children from 1 year of age with active SOJIA in whom other treatments (with anti-inflammatory medicines called NSAIDs and corticosteroids) have not worked well enough, as monotherapy or associated with anti-inflammatory drugs or disease-modifying antirheumatic drugs (DMARDs) according to EMA register document and American College of Rheumatology [Ringold 2013].*
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 ☐ 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). *Only one RCT was found comparing tocilizumab x placebo for SOJIA (n =.112). This RCT reported a benefit with tocilizumab (n=75) when compared to placebo (n=37) at 3 months off follow-up considering clinical response and absence of fever: 85% (64/75) in the treatment group and 24% (9/37) in the placebo group p < 0.001 [De Benedetti 2012].* *A second RCT compared the continuity versus withdraw of tocilizumab for 43 patients achieving an ACR 30 response and a C-reactive protein concentration (CRP) of less than 5 mg/L. Four (17%) of 23 patients in the placebo group maintained an ACR Pedi 30 response and a CRP concentration of less than 15 mg/L compared with 16 (80%) of 20 in the tocilizumab group (p<0.0001). By week 48 of the open-label extension phase, ACR Pedi 30, 50, and 70 responses were achieved by 47 (98%), 45 (94%), and 43 (90%) of 48 patients, respectively. [Yokota 2008].* Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or

	populations (e.g. children, the elderly, pregnant patients)? *The available evidence on low-resource settings is limited.*
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ■ No ☐ Not applicable Comments: *Overall, the safety and adverse effects data is limited due to the paucity of data.* *The application presents the safety assessment from RCT that in its extended phase provided estimate the occurrence of serious adverse events of 25 events/100 patients-year [De Benedetti 2012].* *An observational study reported higher incidence of serious adverse events of 54.5 per 100 patient years [Yokota 2016].*
Are there any adverse effects of concern, or that may require special monitoring?	■ Yes ☐ No ☐ Not applicable Comments: *Concerns about the tuberculosis risk in patients treated with tocilizumab and other biologic DMARD medications is of particular importance in low resource settings with high rates of tuberculosis.*
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 uncertain because of the paucity of data (one small RCT). for efficacy 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 low for relevant outcomes due to 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: *Concerns about the tuberculosis risk in patients treated with tocilizumab and other biologic DMARD medications is of particular importance in low resource settings with high rates of tuberculosis.*
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:
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 SOJIA was found.*

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	*Overall, tocilizumab 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 UK as £11,870.56.* *A Finland cohort-based cost-utility analysis estimated that an additional QALY gained on TCZ cost 15 181 euros when compared with MTX and 14,496 euros when compared with anakinra [Hallien 2014]. A Thailand modelling study estimate a cost of US$35,799 per quality-adjusted life-year (QALY) [Kittiratchakool 2020].*
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 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 uncertain estimates of clinical benefits, 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 tocilizumab on the EML and EMLc.***
References (if required)	*De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367(25):2385-95. doi: 10.1056/NEJMoa1112802. Erratum in: N Engl J Med. 2015 Feb 26;372(9):887.* *Kittiratchakool N, Kulpokin D, Chanjam C, et al. Cost-utility and budget impact analysis of tocilizumab for the treatment of refractory systemic juvenile idiopathic arthritis in Thailand. BMJ Open. 2020;10(9):e037588.* *Hallinen T, Soini EJ, Diamantopoulos A, et al. Cost-utility of tocilizumab in the treatment of systemic juvenile idiopathic arthritis in finland. Annals of the Rheumatic Diseases. 2014.* *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.* *Yokota S, Itoh Y, Morio T, Origasa H, Sumitomo N, Tomobe M, et al. Tocilizumab In systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan. Ann Rheum Dis. 2016;75(9):1654-60.* *Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008 Mar 22;371(9617):998-1006. doi: 10.1016/S0140-6736(08)60454-7.*