A.36 Tocilizumab – systemic onset juvenile idiopathic arthritis

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 incidence of JIA is 1.6-23 per 100,000. There are an estimated more than 2 million children with JIA around the world, most of whom are in Africa and Asia. Joint or extra-articular damage with associated disability are common. If not treated, JIA can result in irreversible physical sequelae and psychosocial impact on quality of life. Approximately 4% to 50% of children with JIA have Systemic Onset JIA (SOJIA), depending on the racial and ethnic groups. SOJIA can be complicated by the serious and often fatal Macrophage Activation Syndrome (MAS) with an uncontrolled ‘cytokine storm’ that has a fatality rate up to 23% (13). Early recognition and treatment of SOJIA is essential to improve outcomes and reduce the risk of MAS. Interleukin 6 inhibitor Tocilizumab has particular advantages in the context of treating MAS. Thus, there is an urgent need to improve access to these medications.

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.

Current treatments of SOJIA include steroids (oral or intravenous) and disease modifying anti rheumatic agents (DMARDs), such as Methotrexate, Anakinra or Tocilizumab. Management with DMARD agents such as Tocilizumab (interleukin-1 inhibitors) or Anakinra (interleukin-1 inhibitors) is now advocated to minimise severe side effects of steroids whilst effectively controlling the underlying disease.

1. Historically, patients with SOJIA were treated with high dose and prolonged courses of glucocorticoids, with significant long-term side effects such as obesity, hypertension, cataracts, and osteoporosis.
2. Methotrexate, while known to be efficacious in many forms of JIA, has a limited role to play in SOJIA in isolation, but is often used in combination with a biologic DMARD such as Tocilizumab.
3. A systematic review and meta-analysis of trials reported that Canakinumab and Tocilizumab are more effective than Rilonacept (another interleukin 1 inhibitor).
4. While anti-tumour necrosis factor alpha agents, (such as Etanercept and Adalimumab, which are already on the WHO Essential Medicines List to treat JIA) have proven efficacy in many other subtypes of JIA, they are not effective for patients with SOJIA. A systematic review including 25 studies with over 4000 patients with JIA, including 1185 with SOJIA, concluded SOJIA appeared to be less responsive to Etanercept when compared to Tocilizumab over 12 weeks (Etanercept: ACR30 58-78% and Tocilizumab: ACR30 85%).
5. A German study showed that those treated with Tocilizumab were less often treated with systemic glucocorticosteroids than those treated with Etanercept when starting the medication (44% vs 83% p<0.001).
6. Rates of adverse events were higher in patients treated with Tocilizumab compared to etanercept (Risk ratio (RR) 5.3/patient year; p<0.0001), and serious adverse events were seen more frequently in those treated with Tocilizumab (RR 2.9; p<0.5) compared to Etanercept, but less than interleukin -1 inhibitors (RR 2.9; p<0.01).
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).

1. 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.

2. 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.

3. 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.

4. A German registry study reported that over a 5-year period, 46 of 200 patients with SOJJA 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.

5. 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.
Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

To date, the evidences of efficacy of Tocilizumab were based on the clinical data from well-resourced settings. Thus, Tocilizumab is a recommended therapeutic choice for children with SOJIA in most well-resourced countries.

**Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?**

- ☒ Yes
- □ No
- □ Not applicable

**Comments:**

The overall rate of adverse events and serious adverse events was 224.3/100 patient years (PYs) and 54.5/100 PYs reported in a Japanese real-world study for 52 weeks and 25/100 PYs and 11/100 PYs in an Italian RCT study for 52 weeks. In a German registry study over a 5-year period, adverse events were seen in 24% and serious adverse events in 4%. Adverse events leading to discontinuation of Tocilizumab occurred in 4.1% of patients (17/417) in the ‘real world’ setting in Japan. The most common adverse events were infections and infestations. Other adverse events included neutropenia, lymphopenia, leukopenia, elevated aminotransferases and macrophage activation syndrome.

A recently published study on long term surveillance of Tocilizumab use in 109 patients with SOJIA, the reported rate of serious adverse events was 21/100 patient years (PY). In particular, cytopenia and hepatic events were seen. Rates of MAS were 2.5 per 100 PY for those treated with Tocilizumab.

**Are there any adverse effects of concern, or that may require special monitoring?**

- □ Yes
- ☒ No
- □ Not applicable

**Comments:**

Any child treated with Tocilizumab (or any biologic DMARD) must have access to urgent paediatric rheumatology review and hospitalisation if they develop serious complications such as infection and MAS, which is of particular importance in low resource countries.

**Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)**

1. The use of Tocilizumab for children with SOJIA improves the short and long term outcomes for these patients based on the evidence from the registry RCT studies and real-world study. In the short term, it allows control of disease with less use of corticosteroids thereby minimising disease morbidity and reducing side effects (of steroids). Early control of disease is important to minimise irreversible damage and in the longer term, control of arthritis leads to an improved functional outcome, with lower rates of deformity, disability and chronic pain.

2. Tocilizumab (Interleukin 6 inhibitor) has particular advantages in the context of treating MAS, a serious and fatal complication of Systemic Onset JIA (SOJIA). SOJIA appeared to be less responsive to Etanercept (anti-tumour necrosis factor alpha agents already on the WHO Essential Medicines List to treat JIA) when compared to Tocilizumab over 12 weeks. Tocilizumab is currently a recommended standard therapeutic choice for children with SOJIA in most well-resourced countries.

3. The most adverse events during Tocilizumab treatment are infections, which also occur during other recommended therapeutic options of SOJIA. The most adverse effects are reversible. Discontinuation of Tocilizumab due to side effects was reported in a minority of patients.
The overall benefit to risk ratio of Tocilizumab is favourable in treatment of SOJIA and sJIA.

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)

The overall quality of the evidence for Tocilizumab as a necessary treatment medicine in children with sJIA is moderate-high. The evidence was based on the results of both RCT study and real-world study and the relatively large number of patients receiving Tocilizumab treatment in the RCT studies and real-world study. However, the evidence is limited in LIMCs. Thus, accumulating data are needed the in real-world study to further assess its efficacy and potential uncommon serious adverse effects in various settings.

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:
All children receiving Tocilizumab will have regular follow up to assess response to treatment and whether there has been adverse event. The frequency of adverse events in patients receiving Tocilizumab is not low. The serious infections can lead to a fatal outcome. Thus, health providers should be trained on how to diagnose sJIA and subtypes, how to recommend and prescribe Tocilizumab in patients with SOJIA, how to recognize and manage the adverse events related to Tocilizumab, how to monitor the laboratory markers and testing during treatment.

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:
Tocilizumab, as a standard treatment option in SOJIA, has been approved by the FDA and EMA for treatment of SOJIA in paediatric patients 2 years of age or older. Tocilizumab appears to be readily available on the market in most countries. In some countries, national registration of Tocilizumab requires the data of local clinical trial study.

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 WHO Guidelines for SJA is published. However, Tocilizumab is recommended for the treatment of SOJIA by the American College of Rheumatology (ACR), the National Institute for Clinical Excellence (NICE), UK, the British Society for Rheumatology and is recommended as part of a consensus-based treatment strategy in Germany.

Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.

Tocilizumab is now readily available on the market and Tocilizumab has been a recommended standard treatment option in SOJIA despite its expensive costs for treatment of SOJIA. The cost-effectiveness analyses from middle ang high income countries reported beneficial cost-effectiveness with better clinical response for the patient, better cost efficiency and reduction of social and economic losses. Thus, the accessibility and affordability of Tocilizumab is not an issue. However, affordability of Tocilizumab remains an issue in low income countries.
### Any additional comments

Tocilizumab is available in Martindale and many other standard medication references. However, Tocilizumab is not found in the Pharmacopeias (The British Pharmacopoeia, The International Pharmacopoeia, The United States Pharmacopoeia, The European Pharmacopoeia). Tocilizumab should be included in the international and national Pharmacopoeia to improve the standard use in different countries.

### 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.

1. Early recognition and treatment of SOJIA is essential to improve outcomes. Interleukin 6 inhibitor Tocilizumab has particular advantages in the context of treating MAS, a serious and fatal complication of SOJIA.
2. The use of Tocilizumab for children with SOJIA improves the short and long term outcomes for these patients.
3. Most of adverse effects can be managed and reversible during Tocilizumab treatment.
4. Tocilizumab has been a recommended standard treatment option in SOJIA.
5. The treatment of Tocilizumab in SOJIA show a beneficial cost-effectiveness in high-income and middle-income countries.
6. Tocilizumab is now readily available on the market.

**Conclusion:** There is an urgent need to improve accessibility and affordability of Tocilizumab in resource-limited countries to enable many children with JIA to be treated to avoid disability and have a better quality of life. Thus, I highly recommend the inclusion of intravenous Tocilizumab on the complementary list of the Model List of Essential Medicines for Children (EMLc) for treatment of SOJIA in pediatric patients 2-17 years of age.

### References (if required)