WHO EML Application

Anakinra

Condition: Systemic Onset Juvenile Idiopathic Arthritis with Macrophage Activation Syndrome.

1

Summary statement of the proposal for inclusion.

The application proposes the inclusion of Anakinra on the complementary list of the EML and the EMLc for the treatment of Systemic Onset Juvenile Idiopathic Arthritis (JIA) with Macrophage Activation Syndrome (MAS).

The rationale for the complementary list is that the use of this drug requires specialised care. The proposed listing on both the EML and EMLc reflects the fact that JIA affects children through adolescence and into adulthood. This rationale is consistent with the listing for the anti-TNF biologics currently listed for JIA.

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of childhood, affecting approximately one per 1000 children (1). JIA is characterised by joint inflammation of more than 6 weeks' duration, with onset before age sixteen years and where no other cause is found (2, 3).

JIA is an autoimmune, non-infective, inflammatory joint disease, the cause of which remains poorly understood with both genetic and environmental contributions (4). It is a distinct entity from rheumatoid arthritis, differing in clinical presentation, prognosis, disease outcomes and treatment approaches. The age of onset in JIA is typically young, with a peak incidence between 1-3 years of age, although the disease persists into adulthood in approximately 50% of cases (5). Even in patients in whom the inflammatory disease resolves, joint or extra-articular damage – with associated disability – are common and if not treated then can result in irreversible sequelae and impact on quality of life (6).

Current treatment approaches for children with JIA aim for normal physical and psychosocial functioning, and with access to modern treatments, good outcomes are an achievable goal for many children with this condition (7). Over recent decades the outcomes for children with JIA have improved substantially. In order to prevent joint destruction, chronic pain and disability, as well as extra-articular complications such as blindness from uveitis (as a complication of JIA), the treatment paradigm for JIA has shifted: earlier, more aggressive therapy with early introduction of disease modifying anti-rheumatic drugs (DMARDs) therapy, and in many cases biological agents, is now the standard of care (3, 8). Notably, initial treatment of polyarticular disease in JIA with NSAID alone is no longer recommended (9). Corticosteroids play a role in the early management of most forms of JIA, but their use in long term health conditions is limited by side their extensive side effect profile (10).

The International League of Associations for Rheumatology (ILAR) recognizes 7 distinct subtypes of JIA; this classification is based primarily on the disease phenotype as well as demographic and serological factors (2, 11). The term JIA replaces Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA) – there are differences in the terminology based on disease presentation and classifications (2, 12). This is important to bear in mind when reviewing the literature and clinical

	studies when different classifications were used. Across the different classifications however the definitions for Systemic Onset disease are essentially the same. **Systemic Onset JIA (SOJIA) subtype - characterised by arthritis, fever, rash and systemic inflammation – warrants particular attention as unlike other JIA subtypes, SOJIA is now recognised as an autoinflammatory syndrome (13, 14). The proportion of children with JIA who have SOJIA ranges from approximately 10% to 50% depending on the population with higher rates being reported in less resourced regions such as India (15). SOJIA can be complicated by the serious and often fatal Macrophage Activation Syndrome (MAS) (14, 16); MAS occurs in 33% of patients with SOJIA (17) and this uncontrolled 'cytokine storm' has a fatality rate up to 23% in SOJIA (18). Early recognition and treatment are essential to improve outcomes (16) including the use of Anakinra as listed in this application. Specific diagnostic criteria for MAS in SOJIA have been developed and validated (19, 20).** **At present, the WHO Essential Medicines List (EML) for JIA does not include the recommended medicines used to manage SOJIA - namely interleukin 6 inhibitor (Tocilizumab) and interleukin-1 inhibitors (Anakinra and Canakinumab). This application focuses on Anakinra and an additional application has been submitted for Tocilizumab; Anakinra has particular advantages in the context of treating SOJIA and MAS and hence the need for both applications. Canakinumab is a long acting form of interleukin-1 inhibitor and also used to treat SOJIA; we have not submitted an application for Canakinumab as this medicine is very expensive.**
2	**Relevant WHO technical department and focal point.** **We have been advised that the Non-Communicable Diseases Department is likely the most relevant technical department.**
3	**Name of organisation(s) consulted and/or supporting the application.** **Please see the attachments in the Appendix; Letter of introduction from the Paediatric Global Musculoskeletal Task Force and Letters of Support from many institutions and organisations from around the world.** **<u>International / National / Regional Organisations</u>** • **Paediatric Task Force for Global Musculoskeletal Health (members of the Task Force have worked together to submit this application)** • **Paediatric Rheumatology European Society** • **Australian and New Zealand Paediatric Rheumatology Group** • **South African Rheumatism and Arthritis Association** • **Paediatric Association for African League of Associations for Rheumatology** • **American College of Rheumatology** • **Childhood Arthritis and Rheumatology Research Alliance** • **Asia Pacific League of Associations for Rheumatology Paediatric Rheumatology Interest Group** **<u>Patient Organisations</u>:** • **Arthritis Kids South Africa** • **European Network for Children with Arthritis** • **Juvenile Arthritis Foundation Australia** • **Versus Arthritis (UK)** **A recent online survey by the Paediatric Global Task Force for Musculoskeletal Health resulted in 97 responses from key opinion leaders in 42 countries (mostly Africa and Asia) to determine the key**

	medicines to treat JIA in their country and health care settings (Scott et al in press and added as an Appendix); >80% respondents deemed the inclusion of Anakinra in the WHO EML to be 'ideal'.
4	**International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.** **INN: Anakinra** **ATC: L04AC03**
5	**Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).** **Anakinra is marketed as Kineret and is available as a 100 mg/0.67 ml solution for injection in a pre-filled syringe.** **The formulation and strength is suitable for use in both paediatric and adult populations.**
6	**Whether listing is requested as an individual medicine or as representative of a pharmacological class.** **We propose Anakinra to be listed as an individual medicine for the treatment of Macrophage Activation Syndrome (MAS) in SOJIA as there are currently no other widely available anti-IL1 products.** **Canakinumab is a long acting form of anti-IL1 and used to treat SOJIA and SOJIA with MAS but is very expensive and not widely available. For this reason we have not submitted an application for Canakinumab to be added to the EML.** **We have submitted another application for Tocilizumab (Il-6)) as a medicine to treat SOJIA without MAS.**

7

Treatment details (requirements for diagnosis, treatment and monitoring).

Systemic onset JIA (SOJIA) is the most severe subtype of JIA, with high grade fevers, rashes, organomegaly, lymphadenopathy, and carries the most significant risk of mortality (14). SOJIA has a highly variable course, with some patients having a monocyclic course of variable length, but the majority will have a chronic course, often with flares and remissions of arthritis, with or without systemic features. The arthritis in SOJIA is usually a polyarthritis and can be very aggressive. MAS is a complication of SOJIA and other inflammatory conditions (17), with high morbidity and potential mortality (16). The diagnosis of MAS in SOJIA is based on defined criteria (16) which have been validated in clinical practice (19, 20). MAS is often triggered by infection, a particular concern in low resource countries, and is a life threatening 'cytokine storm' which has a high risk of mortality (21-23).

It is thought by many that a 'window of opportunity' exists in managing JIA whereby early treatment is more likely to be efficacious (24-28). This emphasises the urgent need to improve access to specialist paediatric rheumatologists (and to essential medicines), in order to limit long-term damage to joints, associated disability and impact on quality of life. An international Task Force of paediatric rheumatologists has stated that the goals of treatment of JIA are to control signs and symptoms, prevent structural damage, to avoid comorbid conditions and drug toxicities, and to optimise function, growth and development, quality of life and social participation (29). However there are significant issues with access to specialist paediatric rheumatologists, multi-disciplinary teams, and treatments, in many low-resource countries and such inequity further contributes to the burden of disease and long term disability (30).

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, growth retardation and osteoporosis. Current treatments of SOJIA include steroids (oral or intravenous) and disease modifying anti-rheumatic agents (DMARDs), such as Methotrexate, Anakinra or Tocilizumab. Methotrexate, whilst known to be efficacious in many forms of JIA, has a limited role to play in SOJIA when used as a sole therapy (21) but is often used in combination with a biologic DMARD such as Tocilizumab.

Management of SOJIA with DMARD agents such as Tocilizumab or Anakinra is now advocated to minimise severe side effects of corticosteroids whilst effectively controlling the underlying disease. The rationale for the use of Tocilizumab or Anakinra in the management of SOJIA is based on several factors including the availability of the medicines. Anakinra however, is the consensus derived medicine of choice for MAS and is included in ACR guidelines (8).

JIA disease activity is now monitored using standard assessment tools and over the decades various tools have been used in clinical practice (31). Increasingly, clinicians and clinical studies have used the Juvenile Arthritis Disease Activity Score (JADAS), which includes: Active Joint Count, Patient/Parent Visual Analogue Scale (VAS) for health status and a Physician/health care provider VAS for disease activity (31). The JADAS also includes blood markers of inflammation (such as CRP and ESR) and there are well defined 'cut-offs' of the JADAS for low disease activity and remission which are the ultimate aim of therapy. Other outcome measures used in studies of JIA include the American College of Rheumatology (ACR) Pedi response criteria (32) based on the core outcome variables for juvenile arthritis (namely, physician global assessment of disease activity (10-cm VAS), parent/patient assessment of overall well-being (10-cm VAS), functional ability, number of joints with active arthritis (defined as joint effusion or limitation of motion accompanied by heat, pain, or tenderness), number of joints with limited range of movement and

ESR.) An ACR (Pedi) 30 response is defined as at least a 30 % improvement from baseline in three of six variables, with no more than one remaining variable worsening by >30 %. Similarly, the ACR Pedi 50, 70, 90, and 100 response definitions require 50 %, 70 %, 90 %, and 100 % improvement, respectively, in at least three core set variables without worsening of more than one variable by >30 %. Conversely, flare is defined as worsening of two variables by at least 40 % without improvement in more than one variable by 30 %. These criteria are currently the 'gold standard' for the assessment of response to therapy in JIA. The ACR Pedi 30 was adapted for use in clinical trials in SOJIA by adding, besides the six core set variables, the demonstration of the absence of spiking fever (>38 °C) during the week preceding the evaluation (33). These measures although useful in studies of SOJIA (and which have been reviewed in our application to the EML for Tocilizumab), are not adequate for the context of SOJIA and MAS; the diagnosis, severity of MAS and monitoring of response to treatment is assessed using blood markers of inflammation (C-reactive Protein and Full blood Counts) as well as specific markers of MAS (Ferritin, Triglycerides, Liver Function Tests and Clotting Profiles) (19, 20). Historical studies of SOJIA have also used the Wallace criteria to define disease activity (31, 34); inactive disease being defined as absence of arthritis, morning stiffness, and systemic features (fever and rash), a physician's global assessment indicating no disease activity (<10 on a scale of 0–100); and normalization of ESR (<20 mm/hour) and CRP level (<10 mg/litre)). We allude further to these measures in the studies described in section 9.

Anakinra is available as a subcutaneous injection. Dosing of Anakinra for SOJIA is based on a child's weight as follows;

- Children < 50 kg: starting dose of 1-2 mg/kg/day
- Children 50kg or more: 100 mg/day.
- In children with inadequate treatment response (often in the context of life threatening MAS) the dose can be escalated up to 4 mg/kg/day.

Treatment with Anakinra may be used short term for the control of acute MAS in SOJIA (e.g. one month) or for the ongoing treatment of SOJIA, especially in cases where Tocilizumab is ineffective or contraindicated (e.g. adverse reaction) or is not available.

Monitoring of Anakinra treatment follows the routine for SOJIA, namely clinical assessment (evidence of systemic features such as rash or fever), evidence of joint inflammation or systemic inflammation elsewhere (such as pericarditis), along with regular monitoring blood tests such as C-reactive Protein and Full blood Counts as well as markers of MAS (Ferritin, Triglycerides, Liver Function Tests and Clotting Profiles) in the event of acute disease flare, concomitant infection or where MAS is suspected (19, 20).

Anakinra can be administered at home for maintenance treatment for SOJIA once patients are well and MAS has resolved. Home administration offers significant benefits in the ease of availability for patients and their families and decreased associated costs (such as day case admission for infusion and staffing requirements). Other than the need for cold storage of Anakinra (between 2- 8 degrees Celsius / 36 - 46 degrees Fahrenheit), no additional costs are anticipated. Patients (and their parents / carers) who are commencing Anakinra require education and support about the administration and storage of the medication at home, as well as regular clinical monitoring and blood tests.

All patients with JIA commencing immunosuppressive treatments should be tested for tuberculosis although in the acute situation of MAS this may not be possible. The ACR recommend that for children at low risk of tuberculosis with negative initial screening test,

	screening should be repeated at any point if their risk of tuberculosis changes to moderate or high, as determined by regional infectious diseases guidelines (8). **Awareness of tuberculosis risk in patients treated with Anakinra or Tocilizumab and other biologic DMARD medications is of particular importance in low resource settings with high rates of tuberculosis; this is emphasised in consensus statements on JIA care in low resource settings as level 3b evidence, strength A statement with 100% consensus (30). It is also recommended that JIA patients with a positive PPD or QuantiFERON test should receive appropriate prophylaxis for tuberculosis (as per their current national/international guidelines) at the start of biologic therapy, when on biologic therapy and a previously negative PPD converts to positive at the mandatory annual tuberculosis screening, and if they have a new exposure to tuberculosis (30).**

8 **Information supporting the public health relevance.**

The incidence of JIA is 1.6-23 per 100,000 (35); 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 most rare subtype of JIA, accounting for approximately 4-9% of cases in European nations, with population study in Norway recording an incidence of 0.6 per 100,000 per year (37). However, it is more common in certain ethnic groups, representing up to 25% and 50% of JIA in India and Japan (14); this corresponds to 312,000 patients with SOJIA in India alone (38). SOJIA is typically a chronic illness affecting young children - the age of onset is typically 1-5 years (39) - 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.

Most epidemiological studies of JIA are from high resource income settings (36). There are an estimated more than 2 million children with JIA around the world, most of whom are in Africa and Asia (40) – these estimates have been derived from known prevalence rates of JIA and modelling using population data for each country. It is acknowledged that the many children with JIA in Asia and Africa are likely to have little or no access to specialist care or medicines (41) and that many children with JIA, have essentially no treatment and this is borne out with worse clinical outcomes in low resource income countries (42). A study describing children with SOJIA treated in Mumbai, India, described high rates of long term complications and damage (43). Children who had a longer duration of time from onset of disease to definitive diagnosis and treatment were more likely to have a chronic/persistent course of disease. In reviewing the treatments offered to these children, 50 of 53 were treated with methotrexate, and 5 had received biologics (3 receiving Tocilizumab and 2 Etanercept), though significantly, none could sustain these treatments for longer than 2 months due to cost considerations. Additionally, 52 of 53 were treated with oral corticosteroids, and 34 were also given pulses of intravenous methylprednisolone. This is in stark contrast to well-resourced countries, where recent trials have focused on commencing DMARDs in steroid-naïve patients, to gain early control of disease and minimise side effects (26).

The consequences of untreated JIA are known from historical studies that predate current approaches to treatment; essentially untreated arthritis results in pain, joint damage, functional disability and impact on quality of life (3, 6, 44) and uncontrolled inflammation carries significant risk of high morbidity and potential mortality from MAS (43). Chronic use of glucocorticoids results in complications (including growth failure, cataracts, osteoporosis) (44). Arthritis involving lower limb joints results in difficulty walking, transferring, getting up from sitting or a squat position and for arthritis involving upper limb joints there are problems with writing, dressing and eating. Untreated JIA results in children missing school, social and peer interactions with long term psychosocial impact, mental ill health and higher unemployment compared to healthy peers (6, 44). The mortality rates in SOJIA are higher than for children with other forms of JIA in the UK (Standardised Mortality Ratio 8.3, 95% CI 2.7 to 19.4 vs 1.7, 95% CI 0.5 to 4.0) (45).

A recent multinational survey of 61 patients and caregivers with SOJIA revealed that even in the biologic era and in well-resourced countries, the burden of disease is significant (46). Although these children were treated with biologics relatively early - mean time from diagnosis to biologic 1.3 years - 54% required at least 1 assistive device, and 20% required home or care alterations. A recent multinational epidemiological study included less

	resourced countries affiliated with the Paediatric Rheumatology International Trials Organisation (PRINTO) indicated that children with JIA in less resourced countries have higher rates of active disease, more joint damage and worse clinical outcomes than their counterparts in high resource countries (31). The social implications are also important, with 36% of caregivers reporting that they had reduced their hours of work or stopped working due to their child's SOJIA, and they lost on average 25 days of work per year. **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. Other key outcomes include linear growth, which can be affected by chronic inflammation, ill health and by medications such as chronic use of glucocorticosteroids. In SOJIA the risk of uncontrolled inflammation and subsequent MAS, which has a high mortality rate, is a particular concern (14, 16).** **There are multiple potential outcomes to consider in assessing the impact of any treatment on a chronic disease such as SOJIA, which include rates of disease flare, rates of MAS and mortality, clinical assessment scores such as Childhood Health Assessment Questionnaire (CHAQ), growth and long-term joint health. Historically, 40% of patients reported at least moderate functional disability (47). In a study of SOJIA patients treated with biologics, mean (±SD) Child Health Questionnaire Parent-Form 50 (CHQ-PF50) physical and psychosocial summary scores were significantly lower in SOJIA patients than a normative population (Physical 40.0 ± 18.2 vs 53.0±8.8; psychosocial 46.6±11.3 vs 51.2±9.1) (46).** **Current treatment approaches for children with SOJIA aim for normal physical and psychosocial functioning, and with access to modern treatments, this is now an achievable goal for many children and joint damage, chronic pain and subsequent disability can be prevented with considerable improvement in quality of life (3). This paradigm shift to earlier, more aggressive therapy with early introduction of disease modifying therapy, is now the standard of care in high resource settings (48, 49). It is therefore more important than ever that the inequity in access to right care is addressed and this is a priority for the paediatric rheumatology community (50); raising awareness, models of care and training to enable the existing workforce to make a diagnosis of JIA and deliver care are the focus of many collaborative initiatives (50). The growth of paediatric rheumatology around the world is gaining momentum; having necessary medicines available through the WHO Essential Medicines List (EML) will be an important step to address inequity and enable many children with JIA to be treated to avoid disability and have a better quality of life.** **At present, the WHO EML for JIA does not include the standard DMARDs used to manage SOJIA - namely interleukin 6 inhibitor Tocilizumab and interleukin-1 inhibitors: Anakinra and Canakinumab. This application focuses on Anakinra for use in MAS as it has particular advantages in this context as detailed in section 9. A separate application has been submitted for Tocilizumab to be used in SOJIA without MAS. Canakinumab is a long acting form of interleukin-1 inhibitor and also used to treat SOJIA / MAS but is not widely used at it is very expensive and hence we have not submitted an application for Canakinumab.**
9	**Review of benefits: summary of evidence of comparative effectiveness**. **PubMed and Google scholar search of paediatric, systemic, Juvenile Idiopathic Arthritis, Macrophage Activation Syndrome, Anakinra.**

There is a paucity of large trials and systematic reviews for Anakinra in SOJIA and MAS.

Clinical trials for Anakinra are described below, as well as a number of systematic reviews and registry studies detailing safety and efficacy data. Due to the small numbers of trials, and small numbers of patients involved, the systematic reviews and meta-analyses review these same individual trials, however all these reviews outline in detail the difficulty of drawing clear conclusions due to variations in outcome measures and datasets. However, despite these limitations, it is worth noting that Anakinra is a recommended therapeutic choice for children with SOJIA and MAS in most well-resourced countries (8, 51, 52).

It is important to note that the most important way to treat MAS in SOJIA is to control the underlying inflammation (of SOJIA). For this reason we will review the evidence for both SOJIA and MAS.

<u>Anakinra in SOJIA</u>

A five year follow up study from the Netherlands which enrolled 42 patients (age range 3.9-11.8 years) with active SOJIA assessed the use of Anakinra as first line monotherapy. The median time to achieve inactive disease (defined as defined according to the modified Wallace criteria (31, 34) as the absence of arthritis, morning stiffness, and systemic features; a physician's global assessment indicating no disease activity (<10 on a scale of 0–100); and normalisation of ESR (<20 mm/hour) and CRP level (<10 mg/litre)) (34, 53) was 33 days. At 1 year, 76% had inactive disease, and 52% had inactive disease while not receiving medication. High neutrophil counts at baseline and a complete response after 1 month of Anakinra were highly associated with inactive disease at 1 year. After 5 years of follow-up, 96% of the patients included had inactive disease, and 75% had inactive disease while not receiving medication. Articular or extraarticular damage was reported in <5%, and only 33% of the patients received glucocorticoids. Treatment with Anakinra was equally effective in SOJIA patients without arthritis at disease onset.

The authors concluded that 'treatment to target' (29), where disease activity is accurately monitored and clinical remission is actively pursued by regular adjustment of therapy (54), starting with first-line, short-course monotherapy with Anakinra), is a highly efficacious strategy to induce and sustain inactive disease and to prevent disease- and glucocorticoid-related damage in SOJIA (28).

A single centre retrospective study from Italy evaluated 25 SOJIA patients treated with Anakinra for at least 6 months (55). Of note these patients had failed therapy with steroids and methotrexate. In this study, 56% of patients reached clinically inactive disease as per inactive disease criteria – defined as the absence of rash, fever and active arthritis (34). Time of onset to start of Anakinra was significantly associated with response with earlier treatment providing significantly improved outcome (55).

An international multicentre series described the use of Anakinra to treat 46 children with SOJIA (56). Amongst 46 patients meeting inclusion criteria, Anakinra monotherapy was used in 10 patients (22%), while 67% received corticosteroids and 33% received additional DMARDs. MAS was present in 20% of these patients (11 episodes in 9 patients), six at onset and 5 during the course of the study. Anakinra effectively managed 5 out of the 6 cases at onset of MAS and increasing doses of Anakinra and additional agents such as steroids and cyclosporin A were used to control these episodes. Anakinra was discontinued for prolonged periods in many of the cases. Outcomes were evaluated at a median follow-up interval of 14.5 months. Fever and rash resolved within 1 month in >95% of patients, while C-reactive protein and ferritin normalized within this interval in >80% of patients. Active arthritis

persisted at 1 month in 39% of patients, at 3 months in 27%, and at >6 months of follow-up in 11%. Approximately 60% of patients, including 8 of 10 receiving Anakinra monotherapy, attained a complete response without escalation of therapy. Disease characteristics and treatment were similar in partial and complete responders, except that partial responders were markedly younger at onset (median age 5.2 years versus 10.2 years; P = 0.004).

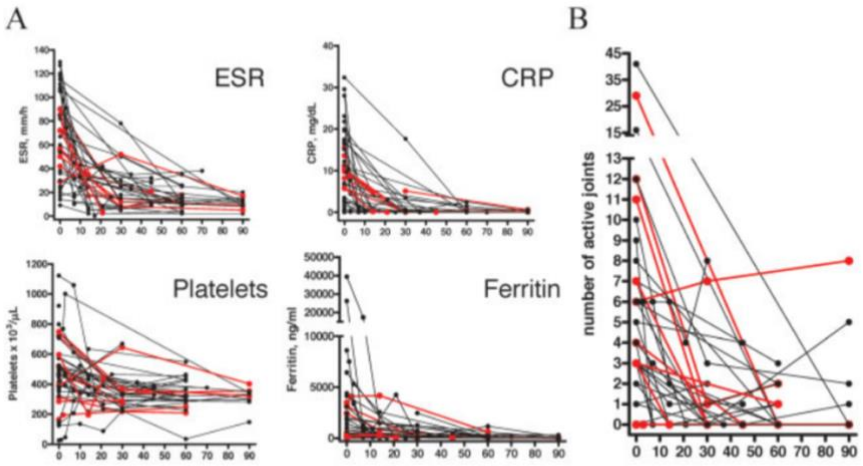

Figure 1. Clinical response in the first 3 months of therapy with anakinra. **A,** Laboratory parameters. **B,** Numbers of joints with active disease. Red lines indicate 10 patients who received anakinra without accompanying corticosteroids or disease-modifying antirheumatic drugs. Numbers on the x-axis refer to days after initiation of anakinra. ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Figure 1 taken from publication (56).

Associated adverse events included documented bacterial infection in 2 patients and hepatitis in 1 patient. The authors concluded that these results supported the use of Anakinra as first line, rather than rescue therapy in SOJIA and that Anakinra has an important role in treating MAS in this context, although in very severe cases of MAS, additional immunosuppressive therapies may be needed.

A retrospective case series of 33 patients from the USA evaluated disease activity and steroid dose in SOJIA. (57) Median duration of SOJIA before treatment was 29 months (range 1-252 months). The vast majority of patients had used more than one other medication before the initiation of Anakinra; this included Prednisone in 94% , Methotrexate in 76%, TNF inhibitors in 61%, Cyclosporin in 36% and Cyclophosphamide in 6%. Treatment was associated with decreases in corticosteroid dosage and sedimentation rate and increases in haemoglobin and albumin (P < 0.02), all indicators of a response to therapy. There were decreases in large joint arthritis counts (P < 0.04) but not small joint counts after 3 to 4 months. There were greater decreases in sedimentation rates from pre to post (1-2 months) in patients on high versus low dose anakinra (P < 0.001) implying a dose response effect. Fever and rash, present in 7 cases before treatment, was resolved in all cases. Eight patients had periods of arthritis, 1 developed MAS, and another Epstein Barr virus infection. This cohort included children with prolonged and established disease and a significant burden of previous medication exposure. Over half of patients reported localized pain or swelling at their injection site.

A small German study from 2012 reported on 4 patients who received Anakinra as first line therapy. Median age was 4.6 years (2.75-9.25). The mean follow-up was 13.5 (range: 2-50) months. Anakinra was started at doses from 1.5 to 4 mg/kg for a median duration of 3 (range: 3-18) months. Two patients responded to Anakinra monotherapy; two cases required corticosteroids. Normalised body temperature and the absence of evanescent rashes were

	achieved after a median of 4 (range: 2-10) days. No treatment-related adverse reactions other than local injection site inflammation were seen. The data suggested rapid efficacy of Anakinra in early SOJIA with reduced treatment related side effects (58). **<u>Macrophage Activation Syndrome in SOJIA</u>** **A Turkish study evaluated the use of Anakinra to treat MAS in 15 paediatric patients (59), 13 with SOJIA and two had other autoinflammatory diseases. Nineteen MAS episodes were observed in these 15 patients. Anakinra (2 mg/kg/day) was started within a median of 1 day after admission. Clinical symptoms resolved, and laboratory findings normalized within median (minimum–maximum) of 2 (1–4) and 6 (4–9) days, respectively after the introduction of Anakinra. Steroid treatment was stopped in a median of 10 (4–13) weeks after the initiation of Anakinra. Patients were followed up for a median of 13 (6–24) months. Two patients developed recurrent MAS episodes when the Anakinra dose was reduced, while the other patients achieved remission. No adverse events were noted (59)** **A study from Canada reported on 12 children with MAS (8 due to SOJIA) who were refractory to Steroids, Cyclosporin A and IVIG (60). Five patients required intensive care. All patients achieved MAS remission after addition of Anakinra within a median of 13 (range 2–19) days. Corticosteroids were discontinued by 6 weeks in seven patients. Patients were followed for a median of 22 (range 2–40) months, and all were in remission of MAS at the final follow-up with excellent control of the underlying rheumatic disease. There were no reported side effects from Anakinra administration.**
10	**Review of harms and toxicity: summary of evidence of safety** **A precise account of patient exposure to date is not possible although Anakinra is used in SOJIA, MAS and a number of other autoinflammatory diseases such as Cryopyrin Associated Periodic Fever Syndrome (CAPS). It is also approved for the treatment of Rheumatoid Arthritis and gout. In general Anakinra has a very satisfactory safety profile.** **A prospective, open-label, single centre, clinical cohort study was conducted at the National Institutes of Health in the USA, from 2003 to 2010, investigating the efficacy and safety of anakinra treatment for up to 5 years in 43 patients with CAPS. There are no direct safety reports on MAS other than in the studies described above. Safety was evaluated using adverse event (AE) reports, laboratory assessments, vital signs and diary reports.(61) In total, 1233 AEs were reported during the study, with a yearly rate of 7.7 AEs per patient. The event rate decreased over time, and dose escalation during the study did not affect AE frequency. Anakinra had similar safety profiles in adults and children. The most frequently reported AEs were typical CAPS disease symptoms such as headache and arthralgia. Injection site reactions occurred mainly during the first month of Anakinra treatment. In total, 14 patients experienced 24 serious AEs (SAEs), all of which resolved during the study period. There were thirteen serious adverse events in seven patients of which seven events occurred in three patients <2 years of age. The most common infections were pneumonia and gastroenteritis, occurring in three and two patients, respectively. The remainder of the serious events were related to post lumbar puncture headaches, performed as part of the study and one episode of MAS triggered by post-operative infection, which resolved with the temporary addition of corticosteroid therapy. Anakinra was not discontinued.**

11 **Summary of available data on comparative cost and cost-effectiveness of the medicine.**

To our knowledge there are no studies of comparative cost of Anakinra in the context of SOJIA MAS which is the focus of this application. Such studies would be challenging at a practical level given the context where affected children with MAS are invariably very unwell and will be cared for in a high dependency / intensive care hospital environment.

We have included a summary table (below) of comparative costs for biological DMARD agents used to treat SOJIA in the UK (62): these are not directly relevant to the context of SOJIA MAS but give an indication of cost of Anakinra as a daily injection compared to the other agents.

	Tocilizumab	**Anakinra**	**Canakinumab**
Unit cost	£228.28 For 162mg SC injection	£183.61 For 100mg SC syringe	£9927.80 for 150mg vial
Dosing for 10kg child	162mg SC every 2 weeks	1-2mg/kg SC daily, up to 4mg/kg daily	4mg/kg SC every 4 weeks
Annual cost 10kg child	£5935.28	£67,017.65	£119,133.60
Dosing for 50kg child	162mg SC weekly	100mg daily, increased if necessary up to 4mg/kg daily (200mg daily)	4mg/kg every 4 weeks (i.e. 200mg)
Annual cost 50kg child	£11,870.56	£67,017.65-134,035.30*	£119,133.60-238,267.20*

***Assuming no vial sharing between patients**

In Australia, Anakinra 100mg SC syringe costs $53 AUD per syringe ($1485 AUD per box of 28). It is not available on the Pharmaceutical Benefits Scheme (PBS) for this indication however through a public hospital a patient will pay no more than $6.60 AUD if they have a government provided concession card or $41 AUD per month if they do not have a concession card. Based on the above example the annual cost of Anakinra in Australia for a 50kg child would be $19345 - $38690 AUD with the patient paying only $79.2 - $492 AUD per year.

In Canada Anakinra, 100mg SC syringe costs approximately $41.101 CAD per syringe with an annual cost for a 50kg child of $15001.5-$3003 CAD.

In the USA prices start from $142.5 USD per syringe making an annual cost for a 50kg child $52012.5-$104025 USD.

It is apparent that the cost of Anakinra across different health care systems is variable and the above are given as examples.

12 **Summary of regulatory status and market availability of the medicine**.

Anakinra is registered in the following markets:

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. **Whilst Anakinra and Tocilizumab are both registered as a treatment for SOJIA, it is not registered as a treatment yet for MAS. Clinical consensus supports Anakinra specifically for MAS and the evidence that is available is detailed in section 9.** **All children receiving Anakinra will have regular follow up to assess response to treatment and whether there has been adverse event(s). A database of patients who have received this drug will be kept on secure hospital databases and in many countries around the world there are registries to collate anonymised data as part of ongoing efficacy and safety monitoring.** **Only clinical personnel appropriately trained and experienced will be involved in the use of this drug to treat SOJIA and MAS. In addition, families need to have education and support to know about the drug, potential side effects and safety concerns and know when to seek health care attention. These principles are based on recommendations and standards of care for JIA (63-65). The inclusion of this drug in the Essential Medicines List therefore has consequences for training of the workforce (to appropriately diagnose, prescribe and administer the drug and support families to store and administer the drug at home). Furthermore, there are implications for the distribution, storage and handling of the drug.** **At this present time, Anakinra is not widely available and there are reports of supply issues over the past few months as the Anakinra has been used as a novel treatment and used in clinical trials for the treatment of Covid-19 related complications that are similar to MAS. The manufacturers are aware of the shortages prior to the pandemic and are working to improve supply and distribution. It is hoped that inclusion on the EML will further add further leverage to support all efforts to improve availability of the drug.**
13	**Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).** **Anakinra is listed in the European Pharmacopoeia.**
14	**Comprehensive reference list and in-text citations.** 1. Harris JG, Kessler EA, Verbsky JW. Update on the treatment of juvenile idiopathic arthritis. Curr Allergy Asthma Rep. 2013;13(4):337-46. 2. Ravelli A, Martini A. Juvenile idiopathic arthritis. The Lancet. 2007;369(9563):767-78. 3. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatology and therapy. 2016;3(2):187-207. 4. Hinks A, Cobb J, Marion MC, Prahalad S, Sudman M, Bowes J, et al. Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. Nat Genet. 2013;45(6):664-9. 5. Sullivan DB, Cassidy JT, Petty RE. Pathogenic implications of age of onset in juvenile rheumatoid arthritis. Arthritis Rheum. 1975;18(3):251-5.

6. Glerup M, Rypdal V, Arnstad ED, Ekelund M, Peltoniemi S, Aalto K, et al. Long-Term Outcomes in Juvenile Idiopathic Arthritis: Eighteen Years of Follow-Up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort. Arthritis Care Res (Hoboken). 2020;72(4):507-16.
7. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile Idiopathic Arthritis: Diagnosis and Treatment. Rheumatol Ther. 2016;3(2):187-207.
8. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, et al. 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 Rheum. 2013;65(10):2499-512.
9. Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken). 2019;71(6):717-34.
10. Batu ED. Glucocorticoid treatment in juvenile idiopathic arthritis. Rheumatol Int. 2019;39(1):13-27.
11. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. The Journal of rheumatology. 2004;31(2):390.
12. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-2.
13. Katsicas MM, Russo RAG. Systemic-Onset Juvenile Idiopathic Arthritis. In: Cimaz R, editor. Periodic and Non-Periodic Fevers. Cham: Springer International Publishing; 2020. p. 65-91.
14. De Benedetti F, Schneider R. Systemic juvenile idiopathic arthritis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. Textbook of Pediatric Rheumatology. 7th ed. Philadelphia: Elsevier; 2016. p. 205-16.
15. Kunjir V, Venugopalan A, Chopra A. Profile of Indian patients with juvenile onset chronic inflammatory joint disease using the ILAR classification criteria for JIA: a community-based cohort study. J Rheumatol. 2010;37(8):1756-62.
16. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun. 2012;13(4):289-98.
17. Cakan M, Karadag SG, Tanatar A, Ayaz NA. The frequency of macrophage activation syndrome and disease course in systemic juvenile idiopathic arthritis. Mod Rheumatol. 2020;30(5):900-4.
18. Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol. 2018;10:117-28.
19. Minoia F, Bovis F, Davi S, Horne A, Fischbach M, Frosch M, et al. Development and initial validation of the MS score for diagnosis of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Ann Rheum Dis. 2019;78(10):1357-62.
20. Shimizu M, Mizuta M, Yasumi T, Iwata N, Okura Y, Kinjo N, et al. Validation of Classification Criteria of Macrophage Activation Syndrome in Japanese Patients With Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2018;70(9):1412-5.

21. Boom V, Anton J, Lahdenne P, Quartier P, Ravelli A, Wulffraat NM, et al. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2015;13:55.
22. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.
23. Collaborators GBDT. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. The Lancet Infectious diseases. 2018;18(3):261-84.
24. Vastert SJ, Jamilloux Y, Quartier P, Ohlman S, Osterling Koskinen L, Kullenberg T, et al. Anakinra in children and adults with Still's disease. Rheumatology (Oxford). 2019;58(Suppl 6):vi9-vi22.
25. Nigrovic PA. Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? Arthritis Rheumatol. 2014;66(6):1405-13.
26. Vastert SJ, de Jager W, Noordman BJ, Holzinger D, Kuis W, Prakken BJ, et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol. 2014;66(4):1034-43.
27. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. Arthritis Res Ther. 2017;19(1):256.
28. Ter Haar NM, van Dijkhuizen EHP, Swart JF, van Royen-Kerkhof A, El Idrissi A, Leek AP, et al. Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. Arthritis Rheumatol. 2019;71(7):1163-73.
29. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Annals of the rheumatic diseases. 2018;77(6):819-28.
30. Scott C, Chan M, Slamang W, Okong'o L, Petty R, Laxer RM, et al. Juvenile arthritis management in less resourced countries (JAMLess): consensus recommendations from the Cradle of Humankind. Clinical rheumatology. 2019;38(2):563-75.
31. Consolaro A, Giancane G, Schiappapietra B, Davì S, Calandra S, Lanni S, et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatric Rheumatology. 2016;14(1):1-8.
32. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1997;40(7):1202-9.
33. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. New England Journal of Medicine. 2012;367(25):2385-95.
34. Wallace CA, Ruperto N, Giannini E, Organization PRIT, Group PRCS. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. The Journal of rheumatology. 2004;31(11):2290-4.
35. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(34):1-222.

36. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014;81(2):112-7.
37. Berntson L, Andersson Gäre B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol. 2003;30(10):2275-82.
38. Janarthanan M. Getting around barriers in biologic treatment for systemic juvenile idiopathic arthritis patients in resource-poor countries. Indian Journal of Rheumatology. 2018;13(1):2-3.
39. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). J Rheumatol. 2008;35(2):343-8.
40. Dave M, Rankin J, Pearce M, Foster HE. Global prevalence estimates of three chronic musculoskeletal conditions: club foot, juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. Pediatric Rheumatology. 2020;18(1):1-7.
41. Chausset A, Pereira B, Echaubard S, Merlin E, Freychet C. Access to paediatric rheumatology care in juvenile idiopathic arthritis: what do we know? A systematic review. Rheumatology. 2020.
42. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. The Lancet Child & adolescent health. 2019;3(4):255-63.
43. Dewoolkar M, Cimaz R, Chickermane PR, Khubchandani RP. Course, Outcome and Complications in Children with Systemic Onset Juvenile Idiopathic Arthritis. Indian J Pediatr. 2017;84(4):294-8.
44. Coulson EJ, Hanson HJ, Foster HE. What does an adult rheumatologist need to know about juvenile idiopathic arthritis? Rheumatology (Oxford, England). 2014;53(12):2155-66.
45. Davies R, Southwood T, Kearsley-Fleet L, Lunt M, Baildam E, Beresford MW, et al. Mortality rates are increased in patients with systemic juvenile idiopathic arthritis. Archives of disease in childhood. 2017;102(2):206-7.
46. Shenoi S, Horneff G, Cidon M, Ramanan AV, Kimura Y, Quartier P, et al. The burden of systemic juvenile idiopathic arthritis for patients and caregivers: an international survey and retrospective chart review. Clin Exp Rheumatol. 2018;36(5):920-8.
47. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol. 2002;29(9):1989-99.
48. Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. Arthritis care & research. 2019;71(6):717-34.
49. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology. 2010;49(7):1406-8.

50. Foster HE, Scott C, Tiderius CJ, Dobbs MB, Ang E, Charuvanij S, et al. Improving musculoskeletal health for children and young people–A 'call to action'. Best Practice & Research Clinical Rheumatology. 2020:101566.
51. British Society for Rheumatology. Tocilizumab use in paediatric and adolescent rheumatology information for health professionals 2020 [Available from: https://www.rheumatology.org.uk/Portals/0/Documents/Guidelines/Paediatric%20guidelines/Tocilizumab_Paediatric_Adolescent_Rheumatology.pdf?ver=2020-03-19-150244-320.
52. Hinze CH, Holzinger D, Lainka E, Haas JP, Speth F, Kallinich T, et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J. 2018;16(1):7.
53. Bowyer SL, Roettcher PA, Higgins GC, Adams B, Myers LK, Wallace C, et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol. 2003;30(2):394-400.
54. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018;77(6):819-28.
55. Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V, et al. Anakinra in Systemic Juvenile Idiopathic Arthritis: A Single-center Experience. J Rheumatol. 2015;42(8):1523-7.
56. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011;63(2):545-55.
57. Zeft A, Hollister R, LaFleur B, Sampath P, Soep J, McNally B, et al. Anakinra for systemic juvenile arthritis: the Rocky Mountain experience. J Clin Rheumatol. 2009;15(4):161-4.
58. Hedrich CM, Bruck N, Fiebig B, Gahr M. Anakinra: a safe and effective first-line treatment in systemic onset juvenile idiopathic arthritis (SoJIA). Rheumatol Int. 2012;32(11):3525-30.
59. Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. Clin Rheumatol. 2018;37(12):3329-35.
60. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology (Oxford, England). 2011;50(2):417-9.
61. Kullenberg T, Löfqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology. 2016;55(8):1499-506.
62. British National Formulary for Children: BMJ Group and Pharmaceutical Press; 2020 [updated September 20202/10/2020]. Available from: https://bnfc.nice.org.uk/medicinal-forms/tocilizumab.html.
63. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford). 2010;49(7):1406-8.

64. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018;77(6):819-28.
65. DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2012;64(7):1001-10.