SMC2104

anakinra 100mg/0.67mL solution for injection in pre-filled syringe (Kineret®)

Swedish Orphan Biovitrum Ltd (SOBI)

7 September 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarized as follows:

ADVICE: following a full submission

anakinra (Kineret®) is accepted for use within NHSScotland.

Indication under review: in adults, adolescents, children and infants aged eight months and older with a body weight of 10kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying anti-rheumatic drugs (DMARDs).

Anakinra was superior to placebo in achieving a modified American College of Rheumatology paediatric (mACRpedi) 30 response in patients with SJIA reliant on corticosteroids for disease control. Anakinra and DMARDs were associated with a similar remission rate in patients with AOSD following eight weeks of treatment.

Chairman
Scottish Medicines Consortium

Indication

In adults, adolescents, children and infants aged eight months and older with a body weight of 10kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.[1]

Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying anti-rheumatic drugs (DMARDs).[1]

Dosing Information

The recommended dose for patients weighing 50kg or more is 100mg/day by subcutaneous (SC) injection. Patients weighing less than 50kg should be dosed by body weight with a starting dose of 1 to 2mg/kg/day.

Response to treatment should be evaluated after one month: In case of persistent systemic manifestations dose may be adjusted in children or continued treatment with anakinra should be reconsidered by the treating physician. In children with inadequate response the dose can be escalated up to 4mg/kg/day.

Alternating the injection site is recommended to avoid discomfort at the site of injection. Cooling of the injection site, warming the injection liquid to room temperature, use of cold packs (before and after the injection), and use of topical glucocorticoids and antihistamines after the injection can alleviate the signs and symptoms of injection site reactions.[1]

For this indication, anakinra treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Still's disease.[1]

Product availability date

25 June 2018

Anakinra meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Anakinra is a recombinant antagonist of the interleukin-1 receptor and inhibits the binding of the pro-inflammatory cytokines interleukin (IL)-1α and IL-1β. This inhibition may reduce the inflammation associated with SJIA and AOSD.[1, 2] Anakinra has previously been reviewed by SMC for rheumatoid arthritis and is not recommended for use in NHSScotland for this indication.

Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD) are rare systemic auto-inflammatory conditions becoming more commonly recognised as a single disease with different ages of onset.

The key evidence to support the use of anakinra was the ANAJIS study[3] in patients with SJIA and the NordicAOSD05 study[4] in patients with AOSD. Supportive evidence included Study 990758[5] in patients with SJIA and two meta-analyses; one in patients with SJIA and one in AOSD.[2, 6]

The ANAJIS study was a multi-centre, phase II, two-part study of patients with SJIA. In part one of the study patients were randomised to one month of treatment with anakinra or placebo. In part two, all patients received open-label anakinra for 11 months.[3, 7] Included patients (aged 2 to 20 years) were required to have greater than six months of disease duration, active systemic disease (disease-related fever and / or C-reactive protein [CRP] greater than 20mg/L and / or first hour erythrocyte sedimentation rate [ESR] greater than 20mm/hour) and significant overall disease activity, as outlined by Quartier et al,[3] at day 1 of the study.[2, 3] Patients were stratified by treatment centre then randomised equally to one month of treatment with anakinra 2mg/kg SC daily, maximum daily dose of 100mg (n=12) or placebo (n=12). Use of DMARDs was not permitted during the study; non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids had to be taken at stable dosage for part one of the study.[2, 3]

The primary outcome was to compare the modified paediatric American College of Rheumatology (mACRpedi) 30 response rates in all patients randomised to treatment with anakinra and placebo following one month of treatment.[8] The ACRpedi was modified for the purpose of this study. A mACRpedi 30 response required a 30% improvement in at least three of the six core criteria for juvenile rheumatoid arthritis and a worsening of 30% or more in no more than one of the core criteria; resolution of systemic symptoms (body temperature less than 38°C over the previous eight days) and a decrease of at least 50% of both CRP and ESR compared with baseline.[2, 3]

The proportion of patients in the anakinra and placebo groups achieving the primary outcome, a mACRpedi 30 response following one month of treatment, was 67% (8/12) and 8% (1/12) respectively, p=0.003.[2, 3]

The proportions of patients in the anakinra and placebo groups respectively with mACRpedi 50 response were 58% and 0%, mACRpedi 70 response were 42% and 0% and no patient in either group had a mACRpedi 100 response at one month.[3] Of the eight patients in the anakinra group who achieved a mACRpedi 30 at one month, only five were still considered responders after two months of treatment. There were no differences in parent / patient reported pain assessments between the anakinra and placebo groups.[3]

NordicAOSD05 was a phase II, open-label, multi-centre study, in patients with refractory, corticosteroid-dependent AOSD who were randomised equally to anakinra (n=12) or a DMARD (n=10) for 24 weeks of treatment. The study included a 28-week open-label extension (OLE), which allowed switching or add-on treatment with the comparator medicine, if improvement did not occur within the 24-week study period.[4] The study enrolled adults with a diagnosis of AOSD, according to Yamaguchi *et al* criteria,[9] and treated with a corticosteroid and possibly a DMARD for at least two months prior to randomisation. Patients had to be considered refractory to corticosteroids and DMARD, defined as need for prednisolone at least 10mg/day (or equivalent) with or without concomitant use of DMARD, and unacceptable disease activity as determined by the investigator. Doses of NSAID and oral corticosteroid had to have been stable for at least two weeks, and doses of DMARD had to be stable for at least four weeks, prior to randomisation.[4] Study medicines were daily anakinra 100mg SC

injection, or methotrexate 10 to 25mg weekly oral/SC/intramuscular, azathioprine 1 to 3mg/kg/day oral, leflunomide 20mg/day oral, ciclosporin 2.5 to 5mg/kg/day in two divided oral doses or sulphasalazine 1000 to 2000mg/day oral. Increases in DMARD dose was allowed following the week 4 assessment. Corticosteroid dosages had to be kept constant for four-weeks following randomisation, and any increases implied treatment failure. Patients were allowed two intra-articular corticosteroid injections in 24 weeks and patient could receive NSAIDs if needed.[4] The primary endpoint was remission of AOSD following eight weeks of treatment with study medicine in all randomised patients. The criteria for AOSD remission required patients to be afebrile (≤37°C body temperature), to have a decrease of CRP and ferritin to within reference limits, to have normal swollen joint counts and normal tender joint counts.[4]

At week 8, 58% (7/12) of patients in the anakinra group and 50% (5/10) in the DMARD group were in remission. The difference between treatments was not statistically significant.[4] The primary and key secondary outcomes are presented in table 1.

Table 1. NordicAOSD05 study; Proportions of patients in remission at week 4, 8 and 24[4]

	Week 4	Week 8*	Week 24
Anakinra (n=12)	50%	58%	50%
DMARD therapy (n=10)	30%	50%	20%

DMARD=disease-modifying anti-rheumatic drug, DMARD therapy included six patients treated with methotrexate, three treated with azathioprine and one treated with leflunomide. The criteria for AOSD remission required; patients to be afebrile (≤37°C body temperature), to have a decrease of CRP and ferritin to within reference limits, to have normal swollen joint counts and normal tender joint counts. *primary endpoint

The mean reductions in prednisolone (or equivalent) dose by week 24 in both the anakinra and the DMARD groups were 10.8 and 10.5mg, respectively. The proportion of patients discontinuing corticosteroids during the study were; 25% (3/12) in the anakinra group and none (0/10) in the DMARD group.[4] There were differences in scores of the patient reported, health-related quality of life questionnaire; Medical Outcomes Study Short-Form 36 (SF-36) physical health summary. A greater number of patients using anakinra reported improvements compared to patients using DMARDs (p=0.011). There were no differences between groups in the SF-36 mental health summary.[4]

In addition to the randomised controlled studies described above, there are a substantial number of published uncontrolled studies of the use of anakinra in patients with Still's disease. Meta-analyses in SJIA and AOSD respectively, reported an ACRpedi 30 response rate of 73% in paediatric patients following 3-months of treatment and a remission rate of 82% in adults. The results from the individual studies included in each meta-analysis were consistent with each other. [2, 6]

Summary of evidence on comparative safety

Anakinra is already licensed for use in rheumatoid arthritis and cryopyrin-associated periodic syndromes, its safety profile for these conditions is established and is supportive of safety in patients with Still's disease.[2] Injection site reactions, transient elevation of liver enzymes, neutropenia and serious infections are described in the anakinra summary of product characteristics (SPC). Reports of macrophage activation syndrome in anakinra treated patients have not been shown to be causal and it is unclear if anakinra should be continued during serious infection to reduce flare risk.[1]

In the ANAJIS study, there were 14 adverse events (AEs) of any grade reported in the anakinra group (n=12) and 13 in the placebo group (n=12) during the one-month double-blind treatment period. NSAIDs and corticosteroids were permitted during the study. No patients reported a serious AE during part-one of the study.[3] The following AEs were reported in the anakinra and placebo groups respectively during part-one of the study (number of events in each group); pain on injection (8 versus 6), post-injection erythema (3 versus 1) and infections (2 versus 2).[3]

In the NordicAOSD05 study, seven of the 12 patients in the anakinra group reported a grade 1 injection site reaction and one patients reported a grade 2 injection site reaction. No patients withdrew from the study because of this.[4]

Study 990758[5] was a prospective, multi-centre study which enrolled 86 patients with JIA, including 15 patients with SJIA. The study enrolled patients aged two to 17 years of age with active poly-articular JIA and on treatment with stable dose methotrexate. If patients were also on treatment with NSAIDs and / oral corticosteroids, they had to be maintained on a stable dose during the study. The first part of the study was a 12-week open-label run-in, during which patients received 1mg/kg/day of anakinra SC (maximum 100mg/day). The second part of the study was double-blind with patients responding to anakinra in part-one randomised to placebo or to continuation of anakinra for 16 weeks. The study protocol was amended with a change in the primary endpoint from efficacy to safety of anakinra in JIA patients due to insufficient enrolment in to the study. The AEs reported in the anakinra (n=25) and placebo (n=25) groups during the double-blind treatment phase were; overall AEs: 68% versus 72%, gastrointestinal related AEs: 32% versus 20%, headache: 24% versus 4%, upper respiratory tract infection: 16% versus 20%, limb pain: 12% versus 16%, fever: 12% versus 8%, and abdominal pain: 12% versus 8%.[5]

Summary of clinical effectiveness issues

Systemic features, including high temperature and rash are prominent at the onset of Still's disease with arthritis developing over weeks and months following disease-onset.[10] Macrophage activation syndrome is a severe, potentially life threatening complication of Still's disease.[11] For some patients with chronic forms of the disease, as the systemic symptoms resolve, arthritis becomes the prominent feature. Some patients will only have a single flare, while others may have intermittent disease.[10] The treatment pathways are different for paediatric and adult-onset. Anakinra may be used as initial therapy or as add-on therapy to corticosteroids for different patients groups within SJIA depending on disease severity. For patients with less severe disease, tocilizumab and DMARDs may be an alternative

to anakinra when used as an add-on therapy.[12, 13] Corticosteroids are the mainstay of treatment and control around 60% of patients with AOSD flare. Approximately 40% to 45% of patients develop corticosteroid dependence and long-term adverse effects.[2, 14] Methotrexate is the first line steroid sparing treatment in AOSD with remission rates of 70% and corticosteroid weaning reported. Anakinra, tocilizumab or canakinumab may be used in patients with refractory disease.[15] Clinical experts consulted by SMC advise that off-label anakinra has been used to treat these conditions in NHSScotland. Anakinra meets SMC orphan equivalent criteria for this indication.

Anakinra was superior to placebo in achieving mACRpedi 30 response in SJIA patients reliant on corticosteroids for disease control in the ANAJIS study.[3] Anakinra and DMARDs were associated with a similar remission rate in AOSD patients following eight-weeks of treatment in the NordicAOSD05 study.[4]

The licensed indication is broader than the evidence described in the ANAJIS and NordicAOSD05 studies.

The ANAJIS study was a very small phase II study, however, there is a limited pool of patients suitable for enrolment in to clinical studies in SJIA. The study did not include patients aged between eight months and up to two years, who are included in the licensed indication, and excluded patients being treated with DMARDs which may limit generalisability for some patients.[8] The EMA highlights it is reasonable to extrapolate efficacy of a medicine to subgroups of children when considerable amounts of data are already available from studies in adults or children with other diseases.[8] Fewer patients in the anakinra group had prior treatment with a DMARD and / or biologic agent: 8/12 versus 11/12.[3] Several patients who had responded to treatment following one month of treatment in the ANAJIS study were not able to maintain that response following subsequent months of treatment. It has been suggested that excluding DMARDs from the study and early corticosteroid tapering may have contributed to this.[3]

The NordicAOSD05 was also a very small phase II study, which was not appropriately powered to show a difference between study treatment and the comparator. The DMARD arm consisted of three different medicines; it is unclear how the DMARDs were selected for each patient and if the DMARDs were titrated up to the most effective dose for each patient. Patients with 'severe' comorbidities, as decided by the investigator, were excluded from the study and may not achieve the same results as patient included in the study. There are no guidelines recommending primary outcome measures for clinical studies in AOSD.

The one month double blind treatment phase of the ANAJIS study and the 24-week controlled phase of the NordicAOSD05 study were too short to evaluate the medium and long-term impact of anakinra on SJIA and AOSD. The meta-analyses provide some additional information however they included uncontrolled studies and were at risk of publication bias.

There are no direct data in relation to biologic comparators, with tocilizumab particularly of interest to Scottish practice. A published indirect treatment comparison (ITC) using the Bucher method, concluded no differences in comparative efficacy (modified ACRpedi 30 response) between anakinra, canakinumab and tocilizumab for the treatment of SJIA.[16] The anakinra study included in the ITC was the ANAJIS study.

Anakinra provides a licenced treatment option for Still's disease. Clinical experts consulted by SMC consider it to be a therapeutic advancement and it may be of particular value in patients who are acutely unwell and in macrophage activation syndrome, a complication of Still's disease.[17] Injection reactions have been reported very commonly with anakinra and the daily injections required could be a disadvantage to some patients.[1]

While anakinra meets SMC orphan criteria in this indication, the company did not request the submission to be assessed under the SMC orphan medicine process.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) comparing anakinra to either canakinumab or tocilizumab in three different patient populations: SJIA paediatric patients weighing 20kg; SJIA patients weighing 50kg; and AOSD patients weighing 70kg. The time horizon for the analysis was one year.

The evidence to support similarity of outcomes between treatments, as is required to use CMA as the appropriate form of economic analysis, was provided by reference to the ITC in patients with SJIA noted above. This was the only source of evidence to support the assumption of similarity between treatments.

Costs in the analysis related to medicines acquisitions costs and the cost of a day hospital appointment for treatment administration for tocilizumab and canakinumab; no treatment administration costs were assumed for anakinra. SMC clinical experts have confirmed that it is reasonable to assume that patients could self-administer. Vial wastage was assumed for treatments where relevant according to the assumed patient weights. PAS discounts are in place for tocilizumab and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS prices.

The base case results are presented in the tables below, at list prices.

Table 2: Comparison with canakinumab:

Patient group	Annual cost anakinra	Annual cost canakinumab	Incremental cost anakinra versus comparator*
Systemic JIA patient 20kg	£9,574	£131,804	-£122,230
Systemic JIA patient 50kg	£9,574	£260,866	-£251,292
Adult onset Still's Disease 70kg	£9,574	£260,866	-£251,292

* A negative sign indicates that the treatment is cost-minimising against the comparator, JIA=juvenile idiopathic arthritis

Table 3: Comparison with tocilizumab: using list price for tocilizumab

Patient group	Annual cost anakinra	Annual cost tocilizumab**	Incremental cost anakinra versus comparator*
Systemic JIA patient 20kg	£9,574	£14,794	-£5,220
Systemic JIA patient 50kg	£9,574	£18,798	-£9,224
Adult onset Still's Disease 70kg	£9,574	£18,798	-£9,224

* A negative sign indicates that the treatment is cost-minimising against the comparator, JIA=juvenile idiopathic arthritis

** assumes a dose of tocilizumab of 400mg every two weeks in 50kg and 70kg patients and 240mg every two weeks in 20kg patients

As noted, the results presented do not take account of the PAS for tocilizumab but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for tocilizumab due to commercial confidentiality and competition law issues.

The company provided additional analysis to test the impact of alternative dosing assumptions for tocilizumab in the adult population (given it is used off-label). While assuming a tocilizumab dose of 8mg/kg every 2 weeks improved the cost-effectiveness result for anakinra compared to those presented above, if a dose of 5mg/kg every 4 weeks was used, anakinra was no longer cost-minimising (at list prices).

There were a number of weaknesses with the analysis:

- The key weakness is the lack of a robust evidence base against the chosen comparators; the only reference provided to support comparable efficacy was the Bucher indirect comparison in SJIA referred to above.
- The company did not initially include tocilizumab as a comparator in the AOSD population, despite noting that it is used routinely as an off-label treatment. Additional analysis was provided on request and is reported above, but note that this assumed a dose of 400mg every 2 weeks and the results would vary depending on the off-label dose used in practice (eg 5 to 8mg/kg every 2 to 4 weeks, with dosing at the lower and less frequent levels resulting in anakinra not being cost-minimising at list prices).
- SMC experts noted some use of corticosteroids and DMARDs in this population, but there was no economic analysis presented versus such treatments. SMC clinical experts also indicate that canakinumab may be a less relevant comparator.

The Committee considered the benefits of anakinra in the context of the SMC decision modifiers that can be applied and agreed that as anakinra is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifier, the Committee accepted anakinra for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from the National Rheumatoid Arthritis Society (NRAS), which is a registered charity.

- NRAS has received 11.6% pharmaceutical company funding in the past two years, including from the submitting company.

- SJIA and AOSD are complex and potentially life-threatening conditions. SJIA can lead to growth retardation, joint contractures, eye problems, destructive joint disease requiring joint replacements, permanent disability and life-threatening sudden hyperactivity of the immune system. SJIA can impair children's personal and social functioning and development. It may also have a considerable impact upon the family of the child. Children often miss out on schooling and normal childhood activities, and as adults they may be limited in, or unable to work. AOSD shares characteristics of systemic-onset juvenile idiopathic arthritis, but it begins in adulthood. It has a similar day to day impact as living with rheumatoid arthritis. Inflammation may affect a few joints at first, but can advance to include more joints over time.

- There are a number of treatments available and many people respond to these but individual treatment responses can vary. In treating such conditions, which are rare but require rapid diagnosis and early treatment, clinicians need to have the freedom to apply their clinical judgement in consultation with the individual/family/parents to ensure the best outcome for the patient.

- Anakinra would provide an additional helpful and effective option to treat SJIA and AOSD. The difference that this medicine could make may be important in terms of improving quality of life, longer term outcomes and impact on families. The possible disadvantage of the requirement for daily injections, particularly for parents of young children who are also on concomitant weekly methotrexate injections, was commented on.

Additional information: guidelines and protocols

Adult-onset Still's Disease

There are no clinical management guidelines for the treatment of AOSD. Jamilloux et al. published a review of treatments for AOSD in 2015 with no conflict of interest declared. The author highlights that suggestions are primarily based on limited evidence from observational studies and treatment is largely empiric. The authors suggest that AOSD can be subdivided in to groups with systemic features or those

with prominent arthritis. NSAIDs are not disease modifying but can be considered in the early stages of disease with less than 20% of patients responding to treatment. The review suggests that corticosteroids are the first line treatment for AOSD and should be commenced immediately once diagnosis is confirmed. Corticosteroids are usually tapered to a stop once symptoms have resolved. Methotrexate may be considered when patients show signs of steroid dependency or when patients are uncontrolled on corticosteroids. Targeted biologic therapies are reserved for AOSD cases refractory to corticosteroid therapy and DMARDs. Anakinra, or alternatively tocilizumab are suggested for patients with refractory AOSD and systemic features. Infliximab, or alternatively tocilizumab if infliximab is not successful/appropriate are suggested for patients with articular AOSD. Anakinra may be used for articular AOSD if earlier options are not appropriate. Other disease modifying anti-rheumatic drugs (DMARDs) such as ciclosporin, leflunomide and azathioprine may be considered but are not recommended unless other medicines have failed or cannot be taken. Intravenous immunoglobulins can be considered in life threatening complications arise or if a flare-up occurs during pregnancy.[15]

In a 2012 article, Pouchot and Arlet made similar suggestions to Jamilloux 2015 for the treatment of AOSD. They suggest that in refractory disease that IL-1 inhibitors (anakinra and canakinumab) may be more effective in systemic manifestations and IL-6 inhibitors (tocilizumab) in arthritis prominent manifestations.[10]

Systemic Juvenile Idiopathic Arthritis

The North American organisation Childhood Arthritis and Rheumatology Research Alliance (CARRA), published consensus treatment plans for new-onset SJIA. Authors declared relationships with the following pharmaceutical companies; Hoffmann LaRoche, Abbott Immunology, Genentech, Biogen Idec Inc., Novartis Pharmaceutical corporation, Centocor, Amgen, Pfizer, and BMS. The publication advises the use of high-dose corticosteroids (oral or IV) for new-onset SJIA with tapering of dose based on severity of disease and response to treatment. For patients unable to reduce their corticosteroid dose by more than 50% following three months of treatment additional therapy with either; methotrexate, tocilizumab or anakinra should be considered.[13] An update was published in 2014 to advise that canakinumab could be considered as an alternative to anakinra for patients requiring adjunctive therapy to corticosteroids.[18]

The American College of Rheumatology (ACR) published updated recommendations in 2013 including recommendations for the medical therapy of children with SJIA.[12] The ACR is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service. The recommendations for initiation of treatment are described separately for different clinical phenotypes of SJIA: a) active systemic features and varying degrees of synovitis, b) no active systemic features and varying degrees of active synovitis, and c) features related to macrophage activation syndrome. Depending on disease severity (considers physician's global assessment tool and active joint count), initial treatment recommendations included NSAIDs (less severe), corticosteroids and anakinra. Patients not obtaining an adequate response to initial one month of treatment with anakinra, could be treated with canakinumab, tocilizumab, methotrexate, leflunomide or a TNF-alpha inhibitor depending on disease severity. Patients not obtaining an adequate response to initial treatment with two weeks of corticosteroid monotherapy are advised to commence one of; anakinra, canakinumab, tocilizumab, methotrexate, or leflunomide depending on disease

severity. Adjunctive systemic and/or intra-articular corticosteroids could be added at any point in the treatment pathways.[12]

Additional information: comparators

Corticosteroids, tocilizumab (off-label for AOSD), methotrexate and canakinumab (not recommended for use by SMC).

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
anakinra	**20 to 100mg SC daily**	**9,548**
canakinumab*	4mg/kg SC every four weeks From 7.5kg	129,061 to 258,123
tocilizumab	Paediatric 8mg or 12mg/kg IV every two weeks Adult** 5 to 8mg/kg IV every two to four weeks	5,325 to 13,312 5,990 to 18,637
methotrexate***	7.5 to 25mg SC weekly 7.5 to 20mg oral weekly (solution) 7.5 to 20mg oral weekly (tablets***)	772 to 961 375 to 1000 8 to 21

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 05 July 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Calculation of adult doses based on a weight of 70kg. Calculation of tocilizumab paediatric doses based on weight range of 12kg to 50kg. *not recommended for use by SMC, **off-label use, ***based on 2.5mg tablets, SC: subcutaneous, IV: intravenous Costs do not take any patient access schemes into consideration.*

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 100 patients per year. Based on an estimated uptake of 56% per year and a 10% discontinuation rate, the impact on the medicines budget was estimated at £481k per year. The net medicines budget impact was estimated at savings of £4.7m per year.

It should be noted that these estimates assumed a considerable proportion of patients were currently being treated with canakinumab, hence the high predicted level of savings. It should also be noted that the calculations do not take into account any PAS discounts for comparator medicines.

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This assessment is based on data submitted by the applicant company up to and including 17 August 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.