

# Tocilizumab for the treatment of systemic juvenile idiopathic arthritis

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Guidance

- 1.1 Tocilizumab is recommended for the treatment of systemic juvenile idiopathic arthritis in children and young people aged 2 years and older whose disease has responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and methotrexate if the manufacturers make tocilizumab (branded or biosimilars) available with the discount agreed as part of the patient access scheme.
- 1.2 Tocilizumab is not recommended for the treatment of systemic juvenile idiopathic arthritis in children and young people aged 2 years and older whose disease continues to respond to methotrexate or who have not been treated with methotrexate.
- 1.3 Children and young people currently receiving tocilizumab for the treatment of systemic juvenile idiopathic arthritis who do not meet the criteria in 1.1 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinicians, and the child or young person and/or their parents or carers.

## 2 The technology

- 2.1 Tocilizumab (RoActemra, Roche Products) is a humanised monoclonal antibody that inhibits the cytokine interleukin-6 (IL-6). Reducing the activity of IL-6 can reduce inflammation in the joints, prevent long-term damage, and improve quality of life and function. Tocilizumab has a marketing authorisation for the treatment of active systemic juvenile idiopathic arthritis (JIA) 'in patients aged 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids'. Tocilizumab can be given as monotherapy (in patients intolerant to methotrexate or if treatment with methotrexate is inappropriate) or in combination with methotrexate.
- 2.2 Upper respiratory tract infection, with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache, is one of the most common side effects of tocilizumab. Other reported side effects include rash, urticaria, diarrhoea, epigastric discomfort and arthralgia. Infusion-related reactions that can be considered serious and life-threatening (such as angioedema) have also been reported. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Tocilizumab is administered as an intravenous infusion over 1 hour and treatment is repeated at 2-week intervals. The recommended dose is 8 mg/kg in patients weighing 30 kg or more, and 12 mg/kg in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. The cost of 80 mg in a 4 ml vial is £102.40 (excluding VAT; 'British national formulary' [BNF] edition 61). The average cost of treatment is £7987.20 per year for a 30 kg patient and £9984 per year for a 25 kg patient, assuming no wastage. The manufacturer of branded tocilizumab (RoActemra, Roche) has agreed a patient access scheme with the Department of Health, which makes tocilizumab available with a discount applied to all invoices. The level of the discount is commercial-in-confidence (for further details see [section 5.2](#)). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published. NHS England

has completed a national procurement for tocilizumab, which includes the biosimilar versions of tocilizumab. Prices paid for the originator or biosimilar tocilizumab should be in line with the national procurement outcome and should be no higher than that provided through the original commercial arrangement.

### 3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of tocilizumab and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

- 3.1 The manufacturer submitted evidence for the two populations defined in the decision problem: population 1 – children and young people aged 2 years and older with systemic JIA that has not responded adequately to prior NSAIDs and systemic corticosteroids; and population 2 – children and young people aged 2 years and older with systemic JIA that has not responded adequately to prior NSAIDs, systemic corticosteroids and methotrexate. For population 1 the manufacturer compared tocilizumab with methotrexate. For population 2 the manufacturer carried out indirect comparisons of tocilizumab with tumour necrosis factor-alpha (TNF-alpha) inhibitors and anakinra.
- 3.2 In the manufacturer's submission, evidence of clinical effectiveness was based on one randomised controlled trial (TENDER). The TENDER trial is an ongoing three-part, 5-year, phase III study. Part one consisted of a 12-week international multicentre randomised double-blind placebo-controlled parallel two-group study to evaluate the efficacy and safety of tocilizumab in children with active systemic JIA. Part two is a 92-week single-group open-label extension and part three is a 3-year single-group open-label continuation of the study. The manufacturer stated that based on the inclusion criteria of the TENDER trial, all participants matched population 1 in the scope. The manufacturer also stated that 95% of TENDER trial participants who were either treated with methotrexate or had had methotrexate in the past matched population 2 in the scope because it was these participants whose disease could be regarded as having responded inadequately to methotrexate. Patients were included in the study if they had symptoms of active disease and the manufacturer stated that 'it follows that if patients have tried in the past or are currently administered methotrexate and continue to have persistent disease then they are inadequate responders'. An inadequate response to methotrexate was defined as patients being on a standard dose of methotrexate for a period of 3 months and still showing symptoms of active systemic JIA at baseline.

- 3.3 TENDER enrolled 112 participants (from 17 countries, including the UK) who were randomised 2:1 to tocilizumab (n = 75) or placebo (n = 37). Tocilizumab was administered every 2 weeks at a dose of 8 mg/kg for participants who weighed at least 30 kg (n = 37) and 12 mg/kg for those who weighed less than 30 kg (n = 38). Ages of patients in the trial ranged from 2 to 17 years, with an average age of 10 years. Patients had to have documented persistent disease activity (at least five active joints, or at least two active joints with fever above 38°C for any 5 out of 14 days of screening) for at least 6 months, and an inadequate response to NSAIDs and corticosteroids because of toxicity or lack of efficacy. An inadequate response to previous treatment was determined by the treating physician's clinical assessment. Before study entry, 78 out of 112 patients (70%) had been treated with methotrexate (36 entered the study on methotrexate that had been previously stopped then restarted; 42 were on their first course of methotrexate, which was ongoing). Approximately 26% (29) of patients were not on methotrexate at baseline but had received and stopped methotrexate previously. Five patients (approximately 5%) had never received methotrexate, and were considered methotrexate naive. Patients taking NSAIDs, corticosteroids and methotrexate were permitted to take part but had to enter the study on a stable dose of the medicines.
- 3.4 The primary outcome measures were the proportion of patients who had a JIA American College of Rheumatology (ACR) 30 response at 12 weeks and absence of fever (defined as no recorded temperature of 37.5°C or above in the preceding 7 days). A JIA ACR30 response is defined as an improvement of at least 30% from the baseline assessments in any three of six core outcome variables, with no more than one of the remaining variables deteriorating by more than 30%. The JIA core outcome variables are: physician global assessment of disease activity (100 mm visual analogue scale [VAS]); parent or patient global assessment of overall well-being (100 mm VAS); number of joints with active arthritis; number of joints with limitation of movement; erythrocyte sedimentation rate; and functional ability (using the Childhood Health Assessment Questionnaire [CHAQ], which measures eight everyday functional activities).
- 3.5 The secondary outcomes were: individual results for each JIA ACR core outcome variable at 12 weeks; JIA ACR 50/70/90 responses at 12 weeks (that is, an improvement of at least 50%, 70% or 90% respectively from the baseline assessments in any three of the six core outcome variables, and no more than



one of the remaining variables worsening by more than 50%, 70% or 90%); corticosteroid reduction; fever; rash; pain; and laboratory outcomes (C-reactive protein [CRP]) levels, anaemia and haemoglobin levels, thrombocytosis and leucocytosis).

- 3.6 Efficacy endpoints were analysed using the intention-to-treat population. All patients were classified as either responders or non-responders. Patients who 'escaped' (patients whose disease did not respond to treatment who switched to an alternative treatment for the disease) or withdrew were classed as non-responders. There was an 'early escape' option to allow children with more severe disease at baseline an opportunity to escape and receive active open-label tocilizumab. Of the 112 patients enrolled, 21 received escape therapy, with 20 of those patients being initially randomised to the placebo arm. The main reasons for escape were fever for at least 3 consecutive days or a JIA ACR30 flare (a worsening of symptoms).
- 3.7 The results of the TENDER trial showed that for its primary endpoint (a JIA ACR30 response and absence of fever at week 12), 85.3% of the tocilizumab patients were classed as responders compared with 24.3% of the placebo patients, a statistically significant difference ( $p < 0.0001$ ). Patients given tocilizumab had a greater chance of achieving JIA ACR30/50/70/90 responses at week 12 in comparison with the placebo patients. The differences in the proportions of tocilizumab patients and placebo patients at each JIA ACR response level were statistically significant ( $p < 0.0001$ ). The proportion of responders showing an ACR30 response was higher in patients receiving tocilizumab 12 mg/kg (97.4%) compared with those receiving tocilizumab 8 mg/kg (83.8%). The efficacy of tocilizumab with respect to individual ACR core outcome variables was analysed as part of the secondary efficacy analyses; these results are marked by the manufacturer of tocilizumab as academic in confidence and therefore are not presented here.
- 3.8 The TENDER trial also included the Child Health Questionnaire (CHQ) as an instrument eliciting patient health-related quality of life. The CHQ assesses a child's physical, emotional and social wellbeing from the perspective of a parent or carer. The questionnaire was completed twice during the randomised period of the study: at baseline (visit 1) and at week 12 (visit 7).

- 3.9 The TENDER trial included data on adverse events. Infusion-related reactions were defined as all events occurring during or within 24 hours of an infusion. In the 12-week controlled phase, 4% of patients from the tocilizumab group experienced adverse events during infusion. One event (angioedema) was considered serious and life-threatening, and the patient stopped study treatment. In the 12-week controlled phase, 16% of patients in the tocilizumab group and 5.4% of patients in the placebo group experienced an adverse event within 24 hours of infusion. In the tocilizumab group, the adverse events included, but were not limited to, rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these adverse events, urticaria, was considered serious. Clinically significant hypersensitivity reactions associated with tocilizumab that meant treatment was stopped were reported in 1 out of 112 patients (less than 1%) treated with tocilizumab during the controlled phase and up to and including the open-label clinical trial.
- 3.10 For the comparison of tocilizumab and methotrexate for population 1, the manufacturer used a post-hoc analysis to compare patients receiving tocilizumab with the 70% of patients in the placebo group who were receiving methotrexate. The manufacturer presented results that showed methotrexate had limited effect on the primary outcome in patients who were in the placebo group and those treated with tocilizumab. The manufacturer concluded that methotrexate as add-on therapy did not have a significant impact on the JIA ACR responses observed in the tocilizumab arms in the TENDER study. The manufacturer further presented results showing that the proportion of patients on tocilizumab who had an ACR30 response was 0.907, compared with 0.154 for those on methotrexate.
- 3.11 No head-to-head trials were available analysing the efficacy of tocilizumab compared with TNF-alpha inhibitors or anakinra for population 2. The manufacturer included data from two studies (Ruperto et al. 2007 [NCT00036374] and the ANAJIS [anakinra in patients with systemic-onset juvenile idiopathic arthritis] study) in the indirect comparison analysis. The NCT00036374 trial compared the TNF-alpha inhibitor infliximab with placebo in patients with juvenile rheumatoid arthritis (systemic 16%, pauciarticular 23%, polyarticular 61%) described as having a suboptimal response to methotrexate. Participants were from North and South America and Europe, aged between 4 and 18 years, and were randomised to infliximab (62 patients) or placebo (60 patients). Patients received concomitant methotrexate alongside placebo or

active treatment. The study was a randomised double-blind placebo-controlled trial, and the primary outcome was the proportion of patients who had a paediatric ACR30 response based on JIA core outcome variables at week 14.

- 3.12 The ANAJIS trial recruited children with systemic JIA and compared anakinra with placebo. This was a multicentre study with 24 participants (12 in each arm) aged 2–20 years, from North America and Europe. The study included patients whose systemic JIA had not responded to methotrexate or any of the disease-modifying anti-rheumatic drugs (DMARDs), and the protocol did not permit the administration of any DMARDs during the trial. The outcomes of the randomised controlled phase were reported after 1 month. The primary outcome was the paediatric ACR score, absence of fever and normalisation of CRP levels and erythrocyte sedimentation rate after 1 month.
- 3.13 The manufacturer undertook an indirect comparison of tocilizumab compared with anakinra. Data from the ANAJIS and the TENDER trials were used. The manufacturer used all patients in the TENDER trial, including those who were methotrexate naive, for the analysis. The relative risk for an outcome of a JIA ACR30 response for patients on tocilizumab compared with anakinra was 2.37 (95% CI 1.10 to 5.10), which was statistically significant. There were no significant differences in JIA ACR30 response and absence of fever between the anakinra and tocilizumab populations. The manufacturer also conducted an indirect comparison of tocilizumab and infliximab using the results from the NCT00036374 trial and the TENDER trial. The outcomes JIA ACR30, 50 and 70 responses were measured. Patients on tocilizumab had a statistically significantly greater chance of having these outcomes than those on infliximab. The relative risks were 2.87 (95% CI 1.49 to 5.55), 5.35 (95% CI 1.91 to 14.97) and 4.61 (95% CI 1.16 to 18.38) for JIA ACR30, 50 and 70 responses respectively.
- 3.14 The manufacturer used an adjustment factor derived from a study of etanercept by Prince et al. (2009). This was an observational study of 146 patients, of whom 27% had systemic JIA. The adjustment factor is the difference in the proportion of responders between the total population with JIA and the subpopulation with systemic JIA. This factor was used to correct for ACR response rates in the indirect comparison results that the manufacturer had derived from the NCT00036374 (infliximab) study (in which 16% of JIA patients had systemic JIA) and the TENDER trial. These resulting ACR response rates were assumed to

represent the responses achieved with all of the TNF-alpha inhibitors.

- 3.15 The manufacturer originally submitted a Markov model to evaluate the cost effectiveness of tocilizumab as part of a sequence of treatments. In the tocilizumab versus methotrexate model, patients progressed to anakinra, etanercept and then adalimumab; in the tocilizumab versus anakinra model, patients progressed to etanercept, adalimumab and then abatacept.
- 3.16 In the manufacturer's original model the Markov chain had 22 states. The model clustered the states into five groups: four groups representing different lines of treatment and the fifth group containing death and uncontrolled disease. Each line of treatment consisted of five health states: ACR responses at the 30, 50, 70 and 90 levels and 'no ACR response'. A patient could move from a particular ACR response in a particular line only to 'no ACR response' in the next line or to death. From 'no ACR response' the patient could move only to one ACR response level within that line of treatment or to 'no ACR response' in the next line. The main assumption of the model was that there were no transitions between ACR response categories (that is, the patient could not move within a given line to a better or worse health state [say, from ACR50 to ACR70]). The analysis assumed that patients stayed in the same health state unless they changed treatment line. After 12 weeks of treatment, the cohort was put on the next treatment in the sequence. Only after being through all four lines did a patient move to the health state 'uncontrolled disease'. The probability of a response or non-response within a line of treatment depended on the treatment. The order in which the treatments were applied did not change these transitions. The probability of death was treatment independent and health-state independent. The probability of withdrawal was health-state independent, but was higher for methotrexate than for other treatment options (all other treatment options had the same probability as each other). All transitions stayed constant over time; that is, they were independent of age or disease duration. In each cycle, the proportion of patients in a given state was calculated. The distribution across states was used to calculate cycle-specific quality-adjusted life years (QALYs) and treatment costs, which were discounted and summed over the length of treatment. The manufacturer's original model had a time horizon of 16 years. This means that a patient in the model starting treatment aged 2 years turned 18 and could be considered an adult at the end of the simulation. The model allowed shorter and longer time durations for sensitivity analysis (up to 30 years). The discount rates

applied were 3.5% for utilities and costs, and costs were considered from an NHS and personal social services perspective. A half-cycle correction was applied.

- 3.17 The initial CHAQ score at baseline for the cohort of patients used in the original economic model was equal to that observed in the TENDER trial. The change in the patient CHAQ score was determined by the level of ACR response after 12 weeks. Improvement in each health state as measured by relative ACR change led to an absolute change in the initial CHAQ score. For a given CHAQ score, a utility was assigned to calculate QALYs. The health-state costs varied with the health state and the treatment costs.
- 3.18 The data inputs for the manufacturer's original model included utility values. To derive utility values, the manufacturer had to map the CHAQ scores to utilities, using a mapping formula derived in adults with rheumatoid arthritis that mapped Health Assessment Questionnaire [HAQ] results onto EQ-5D utilities. The manufacturer recognised that the assumptions that CHAQ is equal to HAQ and that adult EQ-5D is equal to the health-related quality of life of a child are not evidence based, and acknowledged that this mapping method was only used for the analysis to derive QALYs for the economic model because of the lack of other available data.
- 3.19 Treatment costs in the original model were a composite of the cost of the medication and the cost of administering it. For some drugs, the necessary dosage depends on the body weight of the patient. The manufacturer based the unit costs on UK reference costs, literature and expert opinion. The health-state costs depended only on the ACR response level and were independent from any other health outcomes. The manufacturer stated that 'in all comparisons, the identified adverse events are of minor severity and short duration, and their management would have a minuscule cost impact'. Therefore, it can be assumed that they do not have a considerable bearing on the incremental costs of the two model arms.
- 3.20 In response to the preliminary recommendations in the appraisal consultation document, in which the Committee was minded not to recommend tocilizumab, the manufacturer submitted a revised cost-effectiveness Markov economic model. The economic model in the manufacturer's submission was modified such that health states are defined according to categories of CHAQ, rather than being

based on ACR response categories in which an average CHAQ is applied. In the revised economic model the manufacturer adopted an approach in which CHAQ categories define health states. The health states were defined as 'controlled', 'mild', 'moderate' and 'severe'. A simulated patient distribution of CHAQ scores based on the TENDER trial was used to establish the proportion of patients that would fall into each CHAQ category at baseline. The manufacturer used ACR as a potential predictor of the CHAQ score. The manufacturer assigned the following utility values to the health states: 0.19, 0.55, 0.65 and 0.77 to 'severe', 'moderate', 'mild' and 'controlled' respectively.

- 3.21 In the revised economic model, incremental analyses were presented by the manufacturer that compared the sequences of tocilizumab followed by infliximab with infliximab followed by tocilizumab, and then compared tocilizumab followed by anakinra with anakinra followed by tocilizumab followed by anakinra.
- 3.22 When the manufacturer submitted its comments on the appraisal consultation document, it also submitted a patient access scheme, which is a discount on all invoices of tocilizumab. The manufacturer applied the discounted value of tocilizumab to the revised version of the economic model. This document only details the results for tocilizumab with the patient access scheme.
- 3.23 In the manufacturer's revised base-case analyses with the patient access scheme the ICER was £18,194 per QALY gained when tocilizumab followed by infliximab was compared with infliximab alone. When tocilizumab followed by anakinra was compared with anakinra alone, the ICER was £16,923 per QALY gained. The manufacturer conducted two separate incremental analyses for infliximab- and anakinra-containing sequences. In these sequences tocilizumab had been used either before or after infliximab or anakinra and compared with infliximab or anakinra alone respectively. The ICERs obtained when tocilizumab was used first followed by infliximab compared with infliximab alone was £18,194 per QALY gained. For infliximab followed by tocilizumab compared with infliximab alone, the ICER was £30,630 per QALY gained. In the anakinra-containing sequences the ICER was £16,923 per QALY gained when tocilizumab was used first followed by anakinra compared with anakinra alone. Anakinra followed by tocilizumab dominated anakinra alone.
- 3.24 The manufacturer also conducted a sensitivity analysis in the revised model that

included:

- The uncertainty around the adjustment factor derived from the etanercept study used to take account of the other juvenile idiopathic arthritis subgroups in the infliximab study. The base-case sensitivity analysis assuming an increase of the adjustment factor by 30% resulted in an ICER of £20,240 per QALY gained when the tocilizumab then infliximab strategy was compared with infliximab alone. The ICER was £16,923 per QALY gained when the tocilizumab then anakinra strategy was compared with anakinra alone. The respective ICERs when the adjustment factor was decreased by 30% were £16,407 and £16,923 per QALY gained.
- A stopping rule for tocilizumab after treatment duration of 2 years. The base-case sensitivity analysis assuming treatment with tocilizumab was stopped after 2 years. This showed that the tocilizumab then infliximab strategy dominated infliximab alone, and the tocilizumab then anakinra strategy also dominated anakinra alone.
- A decreased frequency of administration of tocilizumab from a 2-weekly regimen to a 4-weekly regimen after treatment duration of 6 months. The resulting ICERs for this base-case sensitivity analysis showed that the tocilizumab then infliximab strategy dominated infliximab alone, and the tocilizumab then anakinra strategy also dominated anakinra alone.

3.25 In response to the preliminary recommendations in the appraisal consultation document, in which the Committee was minded not to recommend tocilizumab, the manufacturer also submitted information on radiographic evidence of progression of joint damage for patients with systemic JIA receiving tocilizumab. The manufacturer stated that the radiographic results from the TENDER trial were not yet available but presented results from a case series (Inaba et al. [2011 and 2007]) that included seven children with a mean age of disease onset of 4.1 years and a mean age of start of treatment of 9.4 years. The mean follow-up of treatment was 56 months. There were radiographic improvements in 57% of joints, worsening in 13% and no change in 30%. The authors of this study noted limitations of the small sample size and radiographic deterioration in some joints, despite stabilisation of systemic inflammatory responses. The authors had concluded that further studies with a larger number of participants were needed. The manufacturer also presented data from a study from Japan (Kaneko et al.

[2009]), which included 46 patients with a mean age of 4 years who had systemic JIA receiving 8 mg/kg of tocilizumab every 2 weeks. The study noted that markers of systemic inflammation and numbers of tender/swollen joint counts were markedly improved following treatment with tocilizumab. However, progression of joint damage was observed in weight-bearing joints such as hip (85%) and knee (57%), along with growth disturbances and osteopenia. Radiographic progression was not seen in small joints.

- 3.26 In response to the preliminary recommendations in the appraisal consultation document, in which the Committee was minded not to recommend tocilizumab, the manufacturer also submitted long-term follow-up data, some of which were marked as academic in confidence and therefore are not presented here. Data from one trial in Japan (Yokota et al. [2005]) in which 11 patients were given tocilizumab every 2 weeks and were followed up for 10–35 months showed that one patient withdrew because of duodenum perforation after 10 months. The authors suggested that this could be because of long-term steroid and NSAID use. The most serious adverse events were pneumonia in 2 patients.
- 3.27 The manufacturer also responded to the Committee's request for clarification on how the CHAQ responses were elicited from the 21 children in the TENDER trial under the age of 5 years. The manufacturer stated that the parents of the children filled in the CHAQ on their behalf.
- 3.28 The ERG noted that the TENDER trial compared tocilizumab plus standard care with placebo plus standard care. The ERG observed that the comparator in this study did not match that specified in the scope and decision problem. For population 1 (that is, children with systemic JIA that has not responded adequately to prior NSAIDs and systemic corticosteroids) the comparator in the scope is methotrexate. The manufacturer, in its submission, had used a post-hoc analysis to compare patients receiving tocilizumab with those patients in the placebo group also receiving methotrexate. The ERG noted that this was not methodologically acceptable because the trial participants were not originally randomised into those populations. In the TENDER trial, 5% of patients were methotrexate naive. The ERG considered that this population would represent population 1 in the decision problem, but the analyses were inadequate. The ERG thus considered that there was insufficient evidence for any comparison of tocilizumab with methotrexate.



- 3.29 For population 2 (children with systemic JIA that has not responded adequately to prior NSAIDs, corticosteroids and methotrexate) the manufacturer's original submission provided data for an indirect comparison of tocilizumab with anakinra, using data from the TENDER trial and a trial of anakinra versus placebo. The ERG considered that the 5% of participants in the TENDER trial who were methotrexate naive should be excluded from these analyses. The manufacturer's original submission only provided data for all participants in the TENDER trial. However, in response to the request for clarification, some data were provided in which methotrexate-naive patients were excluded. These data were not reported for the TENDER trial, but only for the indirect comparison with anakinra. When conducting analyses, the ERG used data for this population when possible. For the comparators, the ERG noted that the manufacturer had decided to broaden the inclusion criteria to include all subtypes of juvenile arthritis, not just systemic JIA. The manufacturer had taken this approach because of the lack of clinical evidence for systemic JIA. The ERG was concerned that this approach had been taken despite the manufacturer's clinical specialists stressing the differences between systemic JIA and other subtypes, and advising against comparing the evidence from different JIA populations.
- 3.30 The ERG also noted the assumption in the original economic model that patients move to a certain ACR response and stay in that state until they either withdraw (move to the next treatment line) or die. The ERG thought that, given the nature of the disease, this assumption was unlikely to be correct.
- 3.31 The ERG noted the lack of health-related quality-of-life data both in the TENDER trial and in the literature, and recognised that very large assumptions (such as assuming that the CHAQ score of a child is equal to the HAQ score of an adult and that adult EQ-5D is equivalent to the health-related quality of life of a child) were needed to assign a utility to each health state in the model. Because of the lack of data in the trial and the literature, the ERG considered the approach used by the manufacturer to be reasonable and acceptable.
- 3.32 The ERG noted the revised modelling approach taken by the manufacturer to address the requests of the Committee after the first Appraisal Committee meeting, regarding the issue of mutually exclusive health states. The ERG considered that by defining health states based on a CHAQ score, and using ACR scores to define the transitions, the revised manufacturer's model does adhere to

common modelling practice. The ERG also noted the manufacturer's approach of linear extrapolation to assigning costs to health states. The ERG did not fully agree with the manufacturer that an individual patient simulation had been performed. However, the ERG was of the opinion that given the purpose of the model, it was an acceptable and practical approach to conduct further economic analyses.

- 3.33 The ERG questioned the cost estimates for health states in the original model as defined by expert opinion, because they present a cost for non-responders (£3300) that is more than six times higher than the cost for an ACR30 response (£500), whereas an ACR90 response is associated with only a 30% decrease in cost (to £350) compared with an ACR30 response. However, in the manufacturer's revised model the ERG considered the linear extrapolation approach to assigning costs to health states to be acceptable.
- 3.34 The ERG noted that the sequences of treatments had been reduced from four treatments in the original model to two treatments in the revised model. The ERG further noted that although there are significant problems in estimating the effect of treatments after first line, it would have been better to have considered all options of including up to four treatments. The ERG conducted exploratory analyses of the full incremental analyses that the manufacturer had presented with the patient access scheme. The ERG's analyses showed that infliximab followed by anakinra compared with infliximab alone resulted in an ICER of £15,819 per QALY gained. The tocilizumab then infliximab strategy compared with the infliximab then anakinra strategy produced an ICER of £22,018 per QALY gained. The tocilizumab then anakinra strategy compared with the tocilizumab then infliximab strategy resulted in an ICER of £67,714 per QALY gained.
- 3.35 Finally, the ERG noted that the revised economic model only allows comparison of two sequences; therefore a probabilistic sensitivity analysis could not be done across all options. The ERG also noted that the manufacturer did not provide the covariance matrix for the regression equation used to determine the correlations between coefficients. The ERG was unable to run a full probabilistic sensitivity analysis. The ERG ran the probabilistic sensitivity analysis twice, once for the infliximab then anakinra strategy compared with infliximab alone, and once for the tocilizumab then infliximab strategy compared with infliximab alone. The ERG noted in its exploratory analyses (which included the patient access scheme and

the probabilistic sensitivity analysis) that the tocilizumab then infliximab strategy resulted in an ICER of £32,331 per QALY gained compared with the infliximab then anakinra strategy. The infliximab then anakinra strategy had an ICER of £22,350 per QALY gained compared with infliximab alone.

- 3.36 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from [www.nice.org.uk/guidance/TA238](http://www.nice.org.uk/guidance/TA238)

## 4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of tocilizumab, having considered evidence on the nature of systemic JIA and the value placed on the benefits of tocilizumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the clinical pathway of care for systemic JIA. The Committee heard that there are currently no other treatments specifically licensed for systemic JIA, although it was noted that etanercept and adalimumab are licensed for polyarticular-course JIA, which would include some patients with systemic JIA. The Committee heard from the clinical specialists that in routine clinical practice in the UK, patients with systemic JIA are treated first with NSAIDs and systemic corticosteroids. If disease activity persists, or if it was severe initially, then methotrexate is used. If the child is intolerant of methotrexate or their condition does not adequately respond to an adequate trial of methotrexate, TNF-alpha inhibitors or anakinra are the next treatment options. It also heard that if there is an inadequate response to these biologicals, other treatment options include tocilizumab, steroid joint injections, high-dose intravenous immunoglobulin, oral ciclosporin, oral thalidomide, autologous stem cell rescue after marrow ablation, and cyclophosphamide.
- 4.3 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical symptoms associated with systemic JIA. The Committee heard that children with systemic JIA experience severe pain and fatigue, and considerable disability. This has a substantial impact on the child's family life, school life, and physical and emotional wellbeing. The condition also has an effect on the wider family, with siblings finding it distressing to see the child living with the condition, and parents and carers often have to stay at home and care for the child if they are unable to attend school. The Committee heard that it was extremely important to control symptoms as quickly as possible to prevent long-term disability in the child. The Committee heard that these children could be prescribed systemic corticosteroids over long periods of time. They could therefore experience increased morbidity and adverse effects that can lead to

chronic conditions including infections, diabetes mellitus, cardiovascular complications and osteoporosis in later life, and risk of long-term joint damage and need for joint replacement. In addition, they may have visible side effects such as growth restriction and Cushing's syndrome. The Committee heard from the clinical specialists and patient experts how tocilizumab had made a dramatic difference to the majority of children who had been treated with it. The Committee heard from the patient expert how tocilizumab had made such a considerable difference to a child's symptoms that the child now had significantly less pain and better energy levels, could take part in everyday activities and sports, and could concentrate sufficiently to participate in school. The Committee also heard that a significant number of children taking tocilizumab had been able to reduce or completely stop using steroids and therefore the visible side effects of the corticosteroid treatment were no longer present.

- 4.4 The Committee heard there is variation in the use of tocilizumab in the UK, but tocilizumab is currently being used for patients whose condition does not respond to methotrexate, or following TNF-alpha inhibitors or anakinra. The Committee heard that the administration of anakinra involves daily subcutaneous injections, compared with an infusion of tocilizumab every 2 weeks. In addition, the Committee heard that, in many instances, although anakinra helps in the short term, its therapeutic effect may degrade whereas the therapeutic action of tocilizumab appeared to be sustained over time. The Committee heard that there was some concern about the unknown long-term effects of tocilizumab, especially in children whose treatment extends into adolescence or early adulthood. The Committee also heard that long-term studies would be needed to confirm that the therapeutic benefits of tocilizumab are sustained in the long term. However, the Committee heard that the magnitude of response to tocilizumab allowed some patients to stop taking the drug until they experienced a further relapse. The Committee also heard that depending on the response, there is the possibility of reducing the frequency of administration from once every 2 weeks to once every 4 weeks. The Committee heard that the peak age of onset of systemic JIA is around 18 months to 2 years, and this age group could potentially benefit most from using tocilizumab.

## Clinical effectiveness

- 4.5 The Committee considered the evidence for the effectiveness of tocilizumab and noted that the manufacturer derived data from the TENDER trial, part one of which was a 12-week randomised controlled trial that compared the efficacy of tocilizumab with placebo. The Committee heard from the clinical specialists that the population was largely generalisable to the UK, but that the mean age of approximately 10 years in the TENDER trial was older than the population they would treat with tocilizumab in routine clinical practice. The Committee concluded that the trial generally reflected the UK population of children with systemic JIA but agreed that the mean age in the trial was older than the population treated in the NHS.
- 4.6 The Committee then considered the evidence for patients whose systemic JIA had not responded to NSAIDs, systemic corticosteroids and methotrexate. The Committee noted that the manufacturer had indicated that in the TENDER trial an inadequate response to methotrexate was defined as patients still showing symptoms of active systemic JIA at baseline despite being on a standard dose of methotrexate for a period of 3 months. The Committee agreed that the 95% of patients in the TENDER trial who were either being treated with methotrexate or had previously been treated with methotrexate could be considered to have disease that had not adequately responded to methotrexate. The Committee therefore concluded that data for these patients should be considered in any comparison of tocilizumab with TNF-alpha inhibitors or anakinra.
- 4.7 The Committee considered the evidence presented for the two populations defined in the scope and the different views of the population definitions from the manufacturer and the ERG. For the population of patients whose systemic JIA had failed to respond to NSAIDs and systemic corticosteroids, the Committee noted that only 5% of the TENDER trial population were methotrexate naive. The Committee also noted that the manufacturer had used a post-hoc analysis to compare patients receiving tocilizumab with those patients in the placebo group receiving methotrexate and that this was not methodologically acceptable. The Committee noted that in practice some patients' systemic JIA would still be responding adequately to methotrexate but no data for these patients had been presented. The Committee therefore concluded that there was no evidence to allow them to further consider the clinical or cost effectiveness of tocilizumab

compared with methotrexate.

- 4.8 The Committee considered the evidence on the clinical effectiveness of tocilizumab in the population who had experienced treatment failure with NSAIDs, systemic corticosteroids and methotrexate. It noted that there were statistically significant improvements in the primary efficacy endpoint (ACR30 response and no fever) and all secondary endpoints at 12 weeks. The Committee was satisfied with the results from the TENDER trial and concluded that tocilizumab was efficacious for the treatment of patients whose systemic JIA had not responded to NSAIDs, corticosteroids and methotrexate.
- 4.9 After requests made at the first Appraisal Committee meeting the Committee noted that radiographic data from the TENDER trial was still unavailable. It also noted that the radiographic progression data from clinical trials presented by the manufacturer were conflicting and the sample sizes of the trials were small, and therefore there was little certainty about the findings for radiographic progression. The Committee concluded that it was possible that patients receiving tocilizumab would experience a delay in the progression of joint damage.
- 4.10 The Committee next considered the manufacturer's indirect comparison of tocilizumab with TNF-alpha inhibitors and anakinra. The Committee noted that the manufacturer used data from the TENDER trial and the NCT00036374 trial to perform an indirect comparison between tocilizumab and infliximab, and used infliximab to represent the class effect of the TNF-alpha inhibitors. The Committee was aware that the NCT00036374 trial was not specifically for patients with systemic JIA and included patients with other subtypes of JIA. However, the Committee noted that patients on tocilizumab were significantly more likely to reach an ACR30 response than patients on infliximab. The Committee also noted the manufacturer presented evidence from the ANAJIS trial that compared anakinra with placebo. The primary outcome measured in the ANAJIS trial was a modified ACR30 response without fever, measured after 4 weeks. The Committee noted that the TENDER and ANAJIS trials were used for an indirect comparison analysis of tocilizumab with anakinra. The Committee also noted that the manufacturer used the whole population from the TENDER trial to represent tocilizumab, whereas the ERG used only the 95% of patients whose condition had not responded to methotrexate. The Committee noted that patients

on tocilizumab were significantly more likely to reach an ACR30 response than patients on anakinra. The Committee also noted that there was no significant difference between tocilizumab and anakinra in terms of ACR30 response plus absence of fever. The Committee concluded from the indirect comparison data that tocilizumab was clinically effective compared with anakinra and infliximab.

## Cost effectiveness

- 4.11 The Committee considered the revised economic model submitted by the manufacturer that included the patient access scheme for cost-effectiveness analysis. The Committee heard how homogenous health states had been defined by CHAQ score and had been categorised as 'controlled', 'mild', 'moderate', and 'severe'. The Committee noted that health states were based on CHAQ scores and regression models had been used to predict expected CHAQ categories using ACR responses. The Committee also noted that there was the possibility that individuals could have the same ACR response and still be in different baseline CHAQ categories, The Committee heard from the ERG that using ACR to define response transitions adhered to common modelling practice. It further noted that the application of the regression model from the 12 week data from the TENDER trial to the baseline CHAQ score to predict 12 week CHAQ values had not been adequately explained. The Committee concluded that although the manufacturer had submitted a revised economic model that represented the natural history of systemic JIA and its response to treatment better than the original model, there were still concerns with some aspects of the model.
- 4.12 The Committee considered the utility values used in the revised economic model. The Committee noted that the manufacturer had identified limitations of the CHQ (which had been used in the TENDER trial to elicit patients' health-related quality of life) and therefore had instead used data from the CHAQ. The manufacturer had made the assumption that the CHAQ score of a child was equal to the HAQ score of an adult and that the adult EQ-5D was equal to the health-related quality of life of a child. The Committee expressed concern about the methods and assumptions that had been used by the manufacturer and considered the utility value of 0.19 assigned to the severe health state in the revised model to be implausible given that approximately two thirds of children entered the model in this state. The Committee heard from the ERG that as most children leave the



severe health state after 12 weeks, this may only have a limited effect on the long-term model. The Committee concluded however that this would over-estimate the incremental QALY gain ascribed to tocilizumab.

- 4.13 The Committee considered the costs for tocilizumab used in the revised economic model. The Committee noted that the costs of treatment were a composite of cost of medication and cost of administering the medication. The Committee heard from the clinical specialists that the costs for the health states in the model were a reasonable reflection of clinical practice in the UK. The Committee concluded that the costs in the model were reasonable, however it noted that potential cost savings could result from reductions in orthopaedic surgery for future joint damage and in bone marrow transplant and stem cell procedures, and that these factors had not been taken into account in the revised model.
- 4.14 The Committee considered the starting age of 5 years in the manufacturer's revised economic model and noted the comment received from a consultee that this was too high. The Committee concluded that the start age in the model was a mean age of 5 years and therefore the spread would include children who were below 5 years of age.
- 4.15 The Committee considered the manufacturer's revised base-case results with the patient access scheme applied. The Committee noted that the anakinra treatment strategies had used the primary outcome of ACR30 response and no fever. The Committee noted that two distinct incremental analyses had been performed: an anakinra-containing strategy that evaluated the strategies of tocilizumab followed by anakinra and anakinra followed by tocilizumab, and how each compared to anakinra alone. The manufacturer had done the same analyses for tocilizumab and infliximab. The Committee heard from the ERG that the incremental analyses the manufacturer presented were not fully incremental. The ERG also noted that the manufacturer's analyses were only designed to compare two technologies with one. The Committee further heard from the ERG that a more rigorous analysis would have involved tocilizumab, infliximab and anakinra in the same sequence using tocilizumab in different places of the sequence. The Committee also noted that as well as not conducting a fully incremental analysis, the manufacturer had not conducted a revised probabilistic sensitivity analysis. The Committee therefore concluded that the manufacturer's cost-effectiveness

estimates could not be considered robust.

- 4.16 The Committee reviewed the ERG's exploratory analyses of the revised model, which included the patient access scheme. The Committee noted the ERG's analysis for the strategy tocilizumab then infliximab, compared with infliximab alone. The Committee considered that this strategy was the most appropriate because tocilizumab is the only licensed technology for systemic JIA and because the strategy of tocilizumab then anakinra compared with anakinra was not considered to be cost effective. The Committee agreed that the ERG's deterministic sensitivity analysis results were preferable to the ERG's probabilistic sensitivity analysis because only a limited number of simulations of the data were run in the probabilistic analysis. Despite the considerable uncertainty around the ICERs, the most plausible ICERs for the strategy tocilizumab followed by infliximab compared with infliximab alone were within a range that would be considered an acceptable use of NHS resources. Given the other factors that had not been taken account of in the manufacturer's model (such as steroid sparing, a decrease in health-related quality of life of the parents or carers, reduction in future orthopaedic surgical operations, bone marrow transplantation and stem cell procedures), on balance, the Committee concluded that the resulting cost-effectiveness estimate would be at the lower end of this range.
- 4.17 The Committee considered the manufacturer's revised sensitivity analyses that included the patient access scheme. The Committee noted the manufacturer's results, and the uncertainty around the adjustment factor derived from the etanercept study used to take account of other types of JIA subgroups in the infliximab study. The Committee noted that an increase or decrease of the adjustment factor by 30% on the tocilizumab then infliximab strategy made only a small difference to the manufacturer's revised base-case ICER. The Committee concluded that the revised model was robust to the sensitivity analyses of the adjustment factor.
- 4.18 The Committee considered the manufacturer's revised scenario analyses including the patient access scheme that looked at the impact of decreasing the frequency of administration of tocilizumab from every 2 to every 4 weeks after a treatment period of 6 months and of stopping tocilizumab after 2 years of treatment. The Committee noted that both scenarios improved the cost effectiveness of tocilizumab further. The Committee had heard from the clinical

specialists that in some instances tocilizumab would be stopped when patients were in complete remission or dose administrations decreased when there was a significant improvement in the patient's condition. The Committee was of the view that when these situations arise in clinical practice that clinicians could consider reducing the frequency of administration of tocilizumab or stop using tocilizumab. The Committee also highlighted the importance of registries in collecting further data on patients receiving tocilizumab so that specific information about long-term outcomes and treatment-related adverse events in systemic JIA can be collected.

- 4.19 In summary, because the Committee did not have any clinical evidence on the comparison of tocilizumab with methotrexate, it concluded that tocilizumab could not be recommended for the treatment of systemic JIA in children and young people aged 2 years and older whose disease continues to respond to methotrexate or who have not been treated with methotrexate. For the population of children whose systemic JIA has not responded adequately to methotrexate as well as NSAIDs and corticosteroids, the Committee accepted the manufacturer's revised model despite its reservations about some aspects of the cost-effectiveness evaluation. The Committee noted the patient access scheme proposed by the manufacturer is a simple discount and would not incur additional costs. Consequently, the Committee concluded that tocilizumab represents a cost-effective use of NHS resources and should be offered as an option for the treatment of systemic JIA in children and young people aged 2 years and older whose condition has inadequately responded to NSAIDs, corticosteroids and methotrexate.

## Summary of Appraisal Committee's key conclusions

TA238	Appraisal title: Tocilizumab for the treatment of systemic juvenile idiopathic arthritis	Section
Key conclusion		

	<ul style="list-style-type: none"> <li>• Tocilizumab is recommended as an option for the treatment of systemic juvenile idiopathic arthritis in children and young people aged 2 years and older whose disease has responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and methotrexate if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme.</li> <li>• Because the Committee did not have any clinical evidence on the comparison of tocilizumab with methotrexate, it concluded that tocilizumab could not be recommended for the treatment of systemic JIA in children and young people aged 2 years and older whose disease continues to respond to methotrexate or who have not been treated with methotrexate.</li> </ul>	<p>1.1 4.19</p>
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard that children with systemic JIA experience severe pain and fatigue, and considerable disability. These children could be prescribed systemic corticosteroids over long periods of time. They could therefore experience increased morbidity and adverse effects that can lead to chronic conditions including infections, diabetes mellitus, cardiovascular complications and osteoporosis in later life, and risk of long-term joint damage and need for joint replacement. In addition, they may have visible side effects such as growth restriction and Cushing's syndrome. The Committee heard from the clinical specialists in the UK, patients with systemic JIA are treated first with NSAIDs and systemic corticosteroids. Methotrexate is then used if disease activity persists. If the child is intolerant of methotrexate or their condition does not adequately respond to an adequate trial of methotrexate, TNF alpha inhibitors or anakinra are the next treatment options to be used.</p>	<p>4.3 4.2</p>
<b>The technology</b>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee heard from the patient expert how tocilizumab had made such a considerable difference to a child's symptoms that the child now had significantly less pain and better energy levels and could concentrate sufficiently to participate in school. The Committee also heard that a significant number of children taking tocilizumab had been able to reduce or completely stop using steroids and therefore the visible side effects of the corticosteroid treatment were no longer present.</p>	<p>4.3</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee heard that there are currently no other treatments specifically licensed for systemic JIA. The Committee heard from the clinical specialists that in routine clinical practice in the UK, patients with systemic JIA are treated first with NSAIDs and systemic corticosteroids.</p> <p>The Committee heard there is variation in the use of tocilizumab in the UK, but tocilizumab is currently being used for patients whose condition does not respond to methotrexate, or following TNF alpha inhibitors or anakinra.</p>	<p>4.2 4.4</p>
<p>Adverse effects</p>	<p>Upper respiratory tract infection, with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache, is one of the most common side effects of tocilizumab. Other reported side effects include rash, urticaria, diarrhoea, epigastric discomfort and arthralgia.</p> <p>Infusion-related reactions that can be considered serious and life-threatening (such as angioedema) have also been reported.</p>	<p>2.2</p>
<p><b>Evidence for clinical effectiveness</b></p>		

<p>Availability, nature and quality of evidence</p>	<p>The Committee considered the evidence for the effectiveness of tocilizumab and noted that the manufacturer derived data from the TENDER trial, part one of which was a 12-week randomised controlled trial that compared the efficacy of tocilizumab with placebo.</p> <p>The Committee noted that the manufacturer used data from the TENDER trial and the NCT00036374 trial to perform an indirect comparison between tocilizumab and infliximab, and used infliximab to represent the class effect of the TNF-alpha inhibitors.</p> <p>The Committee also noted the manufacturer presented evidence from the ANAJIS trial that compared anakinra with placebo.</p> <p>For the population of patients whose systemic JIA had failed to respond to NSAIDs and systemic corticosteroids, the Committee noted that only 5% of the TENDER trial population were methotrexate naive.</p>	<p>4.5 4.10 4.7</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee heard from the clinical specialists that the population was largely generalisable to the UK, but that the mean age of approximately 10 years in the TENDER trial was older than the population they would treat with tocilizumab in routine clinical practice.</p>	<p>4.5</p>

<p>Uncertainties generated by the evidence</p>	<p>The Committee also noted that the manufacturer had used a post-hoc analysis to compare patients receiving tocilizumab with those patients in the placebo group receiving methotrexate and that this was not methodologically acceptable. The Committee noted that in practice some patients' systemic JIA would still be responding adequately to methotrexate but no data for these patients had been presented. The Committee therefore concluded that there was no evidence to allow them to further consider the clinical or cost effectiveness of tocilizumab compared with methotrexate.</p> <p>The Committee noted that the manufacturer used data from the TENDER trial and the NCT00036374 trial to perform an indirect comparison between tocilizumab and infliximab, and used infliximab to represent the class effect of the TNF-alpha inhibitors. The manufacturer used data from the TENDER trial and the ANAJIS trial to perform an indirect comparison between anakinra with placebo.</p>	<p>4.7 4.10</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No clinically relevant subgroups were identified for which there was differential effectiveness.</p>	

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee considered the evidence on the clinical effectiveness of tocilizumab in the population who had experienced treatment failure with NSAIDs, systemic corticosteroids and methotrexate. It noted that there were statistically significant improvements in the primary efficacy endpoint (ACR30 response and no fever) and all secondary endpoints at 12 weeks when tocilizumab was compared with placebo.</p> <p>The Committee noted the evidence and analyses conducted by the manufacturer from the TENDER, NCT0036374 and ANAJIS trials. The Committee noted that patients on tocilizumab were significantly more likely to reach an ACR30 response than patients on anakinra. The Committee also noted that there was no significant difference between tocilizumab and anakinra in terms of ACR30 response plus absence of fever. The Committee concluded from the indirect comparison data that tocilizumab was clinically effective compared with anakinra and infliximab.</p>	<p>4.8 4.10</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The manufacturer provided a revised economic model in which CHAQ categories define health states. The health states were defined as 'controlled' 'mild', 'moderate' and 'severe'. A simulated patient distribution of CHAQ score based on the TENDER trial was used to establish the proportion of patients that would fall into each CHAQ category at baseline. The manufacturer used ACR as a potential predictor of the CHAQ score.</p>	<p>4.11</p>



<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that health states were based on CHAQ scores and regression models had been used to predict expected CHAQ categories using ACR responses.</p> <p>The Committee further noted that the application of the regression model from the 12 week data from the TENDER trial to the baseline CHAQ score to predict 12 week CHAQ values had not been adequately explained. The Committee concluded that although the manufacturer had submitted a revised economic model that represented the natural history of systemic JIA and its response to treatment better than the original model, there were still concerns with some aspects of the model.</p> <p>The Committee expressed concern about the methods and assumptions that had been used by the manufacturer and considered the utility value 0.19 assigned to the severe health state in the revised model to be implausible given that approximately two thirds of children entered the model in this state. The Committee heard from the ERG that as most children leave the severe health state after 12 weeks, this may only have a limited effect on the long-term model. The Committee concluded however that this would over-estimate the incremental QALY gain ascribed to tocilizumab.</p>	<p>4.11 4.12</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The condition has an effect on the wider family, with siblings finding it distressing to see the child living with the condition, and parents and carers often have to stay at home and care for the child if they are unable to attend school. These have not been captured in the model.</p> <p>The Committee noted that certain factors had not been taken into account of in the manufacturer's model such as steroid sparing, a decrease in health related quality of life of the parents and carers, reduction in future orthopaedic surgical operations, bone marrow transplantation and stem cell procedures.</p>	<p>4.3</p> <p>4.16</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Children and young people aged 2 years and older whose disease has responded inadequately to NSAIDs systemic corticosteroids and methotrexate. This is cost effective only if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme.</p>	<p>4.19</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The starting age of treatment of systemic JIA.</p> <p>The potential decrease of frequency of administration of tocilizumab from every 2 to every 4 weeks after a treatment period of 6 months and of stopping tocilizumab 2 years of treatment. The Committee noted that both scenarios were likely to improve the cost effectiveness of tocilizumab.</p>	<p>4.14</p> <p>4.18</p>

Most likely cost-effectiveness estimate (given as an ICER)	Despite the considerable uncertainty around the ICERs, the most plausible ICERs for the strategy tocilizumab followed by infliximab compared with infliximab alone in children and young people aged 2 years and older whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate were within a range that would be considered an acceptable use of NHS resources. Given the other factors that had not been taken account of in the manufacturer's model (such as steroid sparing, a decrease in health-related quality of life of the parents or carers, reduction in future orthopaedic surgical operations, bone marrow transplantation and stem cell procedures), on balance, the Committee concluded that the resulting cost-effectiveness estimate would be at the lower end of this range.	4.16
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	A patient access scheme was submitted by the manufacturer. The level of discount is commercial in confidence	2.3
End-of-life considerations	The supplementary advice was not relevant to this appraisal.	
Equalities considerations and social value judgements	No equalities issues were raised in this appraisal.	

## 5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 The Department of Health and the manufacturer have agreed that tocilizumab will be available to the NHS with a patient access scheme in which tocilizumab for the treatment of systemic JIA will be available with a discount applied to all invoices. The level of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate the level of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Roche Customer Care (0800 731 5711).
- 5.3 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available [on our website](#).
- A costing statement explaining the resource impact of this guidance.
  - Audit support for monitoring local practice.

# Appendix A: Appraisal Committee members and NICE project team

## A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Professor Kathryn Abel**

Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester

### **Dr David Black**

Director of Public Health, Derbyshire County Primary Care Trust

### **Dr Daniele Bryden**

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

### **Dr Andrew Burnett**

Director for Health Improvement and Medical Director, NHS Barnet, London

### **David Chandler**

Lay Member

**Dr Mary Cooke**

Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

**Dr Chris Cooper**

General Practitioner, St John's Way Medical Centre, London

**Professor Peter Crome**

Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

**Richard Devereaux-Phillips**

Director, Public Policy and Advocacy NW Europe, BD, Oxford

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Wasim Hanif**

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

**Dr Alan Haycox**

Reader in Health Economics, University of Liverpool Management School

**Professor Cathy Jackson**

Professor of Primary Care Medicine, University of St Andrews

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

**Professor Eugene Milne**

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

**Dr Neil Myers**

General Practitioner, Glasgow

**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Professor Katherine Payne**

Professor of Health Economics, University of Manchester

**Dr Danielle Preedy**

Lay Member

**Dr Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Dr Surinder Sethi**

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

**Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

**Dr John Stevens**

Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

**Dr Matt Stevenson**

Technical Director, School of Health and Related Research, University of Sheffield

**Professor Paul Trueman**

Professor of Health Economics, Brunel University, London

**Dr Judith Wardle**

Lay Member

## **B NICE project team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and

a project manager.

**Alfred Sackeyfio**

Technical Lead

**Joanna Richardson**

Technical Adviser

**Lori Farrar**

Project Manager



## Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews Ltd:

- Riemsma R, Al MJ, Lhachimi SK et al. Tocilizumab for the treatment of systemic juvenile idiopathic arthritis: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, 2011

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Roche Products

II Professional/specialist and patient/carer groups:

- Arthritis Care
- National Rheumatoid Arthritis Society
- South Asian Health Foundation
- British Health Professionals in Rheumatology
- British Society for Paediatric and Adolescent Rheumatology
- British Society for Rheumatology
- Royal College of Nursing
- Royal College of Paediatrics and Child Health

- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare improvement Scotland
- Abbott
- Pfizer/Wyeth
- Schering-Plough
- Swedish Orphan Biovitrum Ltd
- Arthritis Research UK
- Kleijnen Systematic Reviews Ltd
- National Coordinating Centre for Health Technology Assessment

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on tocilizumab for the treatment of systemic juvenile idiopathic arthritis by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Jeremy Camilleri, Consultant Rheumatologist, nominated by the Welsh Government – clinical specialist

- Dr Mark Wood, Consultant Paediatric Rheumatologist, nominated by the British Society of Paediatric and Adolescent Rheumatology – clinical specialist
- Dr Gavin Cleary, nominated by the British Society of Paediatric and Adolescent Rheumatology – clinical specialist
- Helen Copeland, nominated by the National Rheumatoid Arthritis Society – patient expert
- Sarah Gebbie, nominated by the National Rheumatoid Arthritis Society – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products

# Update information

## June 2024

The wording of the recommendation describing the commercial arrangement (see section 1.1), and in section 2.3, has been updated to include procurement information about tocilizumab biosimilars.

**February 2014:** minor maintenance

**June 2012:** minor maintenance

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