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Tocilizumab for the treatment of rheumatoid arthritis

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NICE technology appraisal guidance 198

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Tocilizumab for the treatment of rheumatoid arthritis

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- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- 'Understanding NICE guidance' – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

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- N2276 (quick reference guide)
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Contents

1 Guidance

1.1 Tocilizumab, in combination with methotrexate, is recommended for the treatment of moderate to severe active rheumatoid arthritis in people whose rheumatoid arthritis has responded inadequately to one or more tumour necrosis factor alpha (TNF-α) inhibitors **and**:

- whose rheumatoid arthritis has responded inadequately to rituximab **or**
- in whom rituximab is contraindicated or when rituximab is withdrawn because of an adverse effect.

1.2 People who are currently receiving tocilizumab for the treatment of rheumatoid arthritis and whose circumstances do not meet the criteria described in 1.1 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Tocilizumab (RoActemra, Roche) is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6). Reducing the activity of IL-6 may reduce inflammation in the joints, prevent long-term damage, improve quality of life and function, and relieve certain systemic effects of rheumatoid arthritis. Tocilizumab, in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has not responded adequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or TNF-α antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by

X-ray and to improve physical function when given in combination with methotrexate.

2.2 Tocilizumab is contraindicated in people with active, severe infections. The summary of product characteristics (SPC) lists the following as the most commonly reported adverse drug reactions associated with tocilizumab treatment: upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased alanine transaminase. For full details of side effects and contraindications, see the SPC.

2.3 Tocilizumab is administered as an intravenous infusion, given over 1 hour. The recommended dosage is 8 mg/kg, given once every 4 weeks. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. Tocilizumab is available in three vial sizes, which are priced at £102.40 for an 80-mg vial, £256 for a 200-mg vial and £512 for a 400-mg vial ('British national formulary' [BNF] edition 59, excluding VAT). The cost for tocilizumab as reported by the manufacturer is £9295 per year for a patient weighing approximately 70 kg. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of tocilizumab, a review of this submission by the Evidence Review Group (ERG; appendix B), and additional analyses by the Decision Support Unit (DSU; appendix B).

Clinical effectiveness

3.1 In the submission, the manufacturer presented evidence on the clinical effectiveness of tocilizumab in combination with DMARDs for two populations: people whose rheumatoid arthritis had

responded inadequately to previous DMARDs but before treatment with a TNF-α inhibitor (that is, a 'DMARD-IR' population) and people whose rheumatoid arthritis had responded inadequately to previous TNF-α inhibitors but before treatment with rituximab (that is a 'TNF-IR' population). The manufacturer also presented evidence on the clinical effectiveness of tocilizumab as monotherapy. The submission focused on the tocilizumab 8 mg/kg treatment arms of the included studies because this is the recommended dose in the SPC. Some of the studies also included doses other than the licensed dose. Results for doses other than the licensed dose are not considered in this appraisal.

Tocilizumab plus DMARDs as an additional treatment before a TNF-α inhibitor

3.2 The main clinical-effectiveness evidence for the DMARD-IR population came from three randomised controlled trials (RCTs). All three RCTs were randomised, double-blind, placebo-controlled parallel-group studies in adults with moderate to severe active rheumatoid arthritis whose condition had responded inadequately to treatment with methotrexate (OPTION and LITHE) or traditional DMARDs (TOWARD). The OPTION trial assessed the effects of tocilizumab 8 mg/kg plus methotrexate (n = 205) compared with placebo plus methotrexate (n = 204). The LITHE trial assessed the effects of tocilizumab 8 mg/kg plus methotrexate (n = 398) compared with placebo plus methotrexate (n = 393). The TOWARD trial assessed the effects of tocilizumab 8 mg/kg plus DMARDs (n = 805) compared with placebo plus DMARDs (n = 415).

3.3 The primary outcome in the RCTs was the proportion of people with an American College of Rheumatology (ACR) 20 response at week 24. This was defined as at least a 20% improvement in both the tender joint count and the swollen joint count and at least a 20% improvement in three of the other five core set measures included in the ACR score. In all three RCTs, the same outcome

measure and data collection instruments were used. The manufacturer stated that the RCTs had similar patient populations. This was demonstrated by general demographics and the effect of various factors on the ACR20 response rate, which was examined by logistic regression analysis. No significant differences were found in treatment effects between studies and the manufacturer inferred that pooling the results of the three RCTs for the primary outcome was appropriate. The manufacturer's submission stated that the adjusted odds ratio for the ACR20 response of tocilizumab 8 mg/kg plus DMARD compared with placebo plus DMARD was approximately 4.2. Averaged ACR20 response rates, described as pooled results, were 59.2% in the tocilizumab 8 mg/kg arm compared with 25.8% in the placebo arm ($p \leq 0.0001$) at week 24.

3.4 Secondary outcomes of the RCTs, measured at 24 weeks, were pooled across the three RCTs by the manufacturer. Pooled ACR response rates were: 37.0% compared with 9.6% for ACR50 response rates ($p < 0.0001$), 18.5% compared with 2.4% for ACR70 response rates ($p \leq 0.0001$), and 4.2% compared with 0.3% for ACR90 response rates ($p \leq 0.0001$), for the tocilizumab 8 mg/kg plus DMARD arms and placebo plus DMARD arms respectively. The manufacturer also presented averaged disease activity score 28 (DAS28) results from the three RCTs. Approximately half of all people in the RCTs reached low disease activity, defined as DAS28 of less than 3.2. Approximately one-third of people in the RCTs went into remission, defined as DAS28 of less than 2.6. The proportion of patients going into remission while on tocilizumab was reported to increase during the study period. There was a greater decrease in averaged health assessment questionnaire (HAQ) results from baseline HAQ score in the tocilizumab groups than with placebo. In the pooled population at week 24, the proportion of patients with a clinically relevant improvement in HAQ (defined as a decrease of at least 0.25 in an individual's total score) was higher in the tocilizumab groups (68%) than in the placebo groups (52%).

3.5 Additionally, European quality of life (EuroQoL) health-state questionnaire (EQ-5D) scores were collected in the OPTION and LITHE RCTs. In the OPTION RCT, the baseline mean EQ-5D was 0.393 (standard deviation 0.327) in the tocilizumab 8 mg/kg plus methotrexate arm, and 0.391 (standard deviation 0.329) in the placebo plus methotrexate arm. At follow-up, the mean EQ-5D was 0.671 (standard deviation 0.237) in the tocilizumab 8 mg/kg arm and 0.534 (standard deviation 0.318) in the placebo arm. The manufacturer did not provide EQ-5D results from the LITHE RCT separately by treatment arm.

3.6 Two single-arm extension studies assessed maintenance of clinical benefit of tocilizumab beyond 24 weeks. Overall, response rates for those remaining on tocilizumab plus DMARD treatment were maintained or continued to improve with duration of treatment, with an increasing proportion of people achieving higher ACR scores over time. The manufacturer reported that improvements in HAQ scores were observed for up to 132 weeks in the pooled tocilizumab 8 mg/kg plus DMARD arm.

3.7 No head-to-head studies were identified that provided evidence on the clinical effectiveness of tocilizumab compared with TNF-α inhibitors, abatacept or rituximab for the DMARD-IR population. Therefore, the manufacturer conducted a mixed treatment comparison. A total of 18 RCTs (including the OPTION, LITHE and TOWARD trials) were identified for inclusion. All studies were randomised, placebo-controlled, double-blind trials and all had a follow-up period of either 24 or 30 weeks. Patients included were predominantly female (approximately 80%), older than 50 years, had experienced more than 6 years' duration of rheumatoid arthritis, were previously treated with an average of two or more DMARDs, and more than half had used non-steroidal anti-inflammatory drugs or glucocorticoids concomitantly. The manufacturer reported that the baseline characteristics across the

trials were comparable with respect to ACR core parameters. Results for TNF-α inhibitors were pooled, because it was assumed there was no difference in efficacy between these drugs. This assumption was reported to be informed by 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130).

3.8 The mixed treatment comparison suggested that tocilizumab showed efficacy (measured by ACR20 and ACR50 response rates) comparable to all included biological treatments. For the ACR70 response rate, tocilizumab treatment was associated with a higher response rate than the TNF-α inhibitors and abatacept (relative risks of 1.77 and 1.98 respectively) and was comparable to rituximab. In the base-case comparison, there was a greater than 99% probability that tocilizumab was more efficacious than biological treatments (that is, etanercept, infliximab, adalimumab and rituximab), as measured by ACR70 response rates. The manufacturer stated that homogeneity at each ACR response level was assessed using Cochran's Q-statistic (ACR20: 44.1857, $p = 0.0002$; ACR50: 41.6878, $p = 0.0004$; ACR70: 25.5752, $p = 0.0603$). Based on these results, the manufacturer used random-effects methods to estimate ACR20 and ACR50 response rates, and fixed-effect methods to estimate ACR70 response rates. As well as the base-case mixed treatment comparison, the manufacturer also presented three scenario analyses, which included or excluded data from certain trials included in the base case. The manufacturer stated that overall the results from these alternative scenarios were consistent with the initial findings.

Tocilizumab plus DMARDs as an additional treatment before rituximab

3.9 The main clinical-effectiveness evidence for the TNF-IR population came from one RCT, known as RADIATE. RADIATE was a randomised, double-blind, placebo-controlled, parallel-group study

in adults with moderate to severe rheumatoid arthritis. The participants' rheumatoid arthritis had responded inadequately to previous TNF-α inhibitor therapy. RADIATE assessed the effects of tocilizumab 8 mg/kg plus methotrexate (n = 170) compared with placebo plus methotrexate (n = 158).

3.10 The primary outcome of the RADIATE trial was ACR20 response rate. At 24 weeks, 50% of patients in the tocilizumab arm compared with 10% of patients in the placebo arm had experienced an ACR20 response ($p < 0.0001$). Additionally, at 24 weeks, 28.8% compared with 3.8% had experienced an ACR50 response ($p < 0.0001$), and 12.4% compared with 1.3% had experienced an ACR70 response ($p < 0.0002$), for the tocilizumab arm and the placebo arm respectively. At week 24, the mean change from baseline in DAS28 was −3.16 for tocilizumab and −0.95 for placebo. The manufacturer stated that the remission rates were similar to those seen in the DMARD-IR population at 24 weeks. The mean decrease in HAQ from baseline at 24 weeks for the tocilizumab group was 0.39, compared with 0.05 for the placebo group.

3.11 Two single-arm extension studies assessed the maintenance of clinical benefit of tocilizumab plus DMARDs beyond 24 weeks. Response rates to therapy with tocilizumab were maintained or continued to improve with duration of treatment (as in the DMARD-IR population). Results similar to those for the DMARD-IR population were reported and the manufacturer noted that the pattern of improvement in mean HAQ score was also observed for up to 132 weeks.

Tocilizumab as a monotherapy

3.12 One RCT, known as AMBITION, assessed the effects of tocilizumab 8 mg/kg alone (n = 288) compared with methotrexate alone (n = 284). This was a double-blind, placebo-controlled trial that included a sub-study tocilizumab arm in which placebo was

given first for 8 weeks and then tocilizumab was given for 16 weeks. Most of the people in the AMBITION RCT had not received treatment with methotrexate before or had stopped methotrexate treatment for reasons other than toxicity or lack of efficacy.

3.13 The ACR20 response rate at 24 weeks in the intention-to-treat population was 69.9% in the tocilizumab arm compared with 52.5% in the methotrexate arm. The weighted difference in ACR20 response was 0.19 (95% confidence interval 0.11 to 0.27). The manufacturer concluded that treatment with tocilizumab was non-inferior to treatment with methotrexate. The manufacturer also stated that the trial population of AMBITION was not in accordance with the SPC of tocilizumab. This was because the AMBITION trial had recruited people who had not received any previous treatment with methotrexate; the SPC states that tocilizumab can be given as monotherapy in case of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate.

Adverse events

3.14 The manufacturer reported that adverse events associated with the mechanism of IL-6 receptor (IL-6R) inhibition were observed in all tocilizumab treatment groups. These adverse events included transient hepatic transaminase elevations, asymptomatic elevations of indirect bilirubin, transient neutropenia, and lipid elevations that appear to occur in association with marked decreases in acute phase proteins. In addition, serious infections associated with the immunomodulatory effects of tocilizumab were comparable to the incidence of serious infections with TNF-α inhibitors. Adverse events reported more frequently with tocilizumab 8 mg/kg monotherapy than in the methotrexate group were abdominal pain and discomfort, headache, dizziness, rash, pruritis and elevated blood pressure, neutropenia, leukopenia and hyperlipidemia. Most of these events were mild and transient. The manufacturer reported

that there was no increase in the severity or frequency of adverse events with prolonged exposure to the tocilizumab 8 mg/kg dose.

Follow-up data

3.15 In addition to the original submission, the manufacturer of tocilizumab provided updated data with a maximum of 180 weeks of follow-up. The response rates of all people who received at least one dose of tocilizumab in the OPTION, AMBITION, RADIATE and TOWARD trials were analysed. A total of 3986 people were included in the long-term analyses. Approximately 14% of people discontinued tocilizumab treatment for safety reasons (including intercurrent illness). The manufacturer stated that tocilizumab increased or maintained ACR response rates in the DMARD-IR, TNF-IR and tocilizumab monotherapy populations. This was demonstrated by the increased proportion of people with ACR50 and ACR70 responses and with an ACR70 response maintained for 24 consecutive weeks. The manufacturer also used the long-term follow-up data to re-estimate the HAQ progression with tocilizumab. The manufacturer stated that there was a negative trend (an improvement) in HAQ progression for both the DMARD-IR and TNF-IR populations.

Cost effectiveness

3.16 The manufacturer did not identify any economic evaluations of tocilizumab and developed a de novo economic model for the submission. This was an individual sampling model with a hypothetical homogenous cohort. The model used a lifetime horizon for costs and benefits. It considered the DMARD-IR and TNF-IR populations separately. No evidence on the cost effectiveness of tocilizumab monotherapy was presented.

3.17 The manufacturer's economic model compared a treatment sequence that included tocilizumab with the same treatment sequence without tocilizumab for two populations. For the

DMARD-IR population, tocilizumab plus methotrexate was the first biological treatment and if the condition did not respond or if the ACR20 response rate was no longer achieved then etanercept plus methotrexate was the next treatment. This was followed by rituximab plus methotrexate, then leflunomide, then gold, then ciclosporin until people withdrew from the last treatment (ciclosporin) and moved on to palliative care. The sequence was the same for the comparator arm, but excluded tocilizumab plus methotrexate at the beginning. For the TNF-IR population, the sequence was the same as the DMARD-IR population, except for the omission of etanercept plus methotrexate (that is, the first treatment in the comparator arm was rituximab plus methotrexate).

3.18 The probabilities of response were derived from the adjusted ACR response rates (adjusted for placebo differences across trials) from the base-case mixed treatment comparison. There were four categories of response: non-response, ACR20 response, ACR50 response, and ACR70 response. Patients were assigned a predefined drop in HAQ score (that is, an improvement in physical function) based on their ACR responses. Data from four RCTs (OPTION, TOWARD, LITHE and RADIATE) were analysed to estimate the relationship between ACR response and HAQ score in the first 24 weeks. Those patients whose condition responded were assumed to have a constant probability of withdrawal owing to lack of efficacy. The probability of withdrawing from treatment was the same for the biological treatments (that is, infliximab, etanercept, adalimumab, rituximab and tocilizumab) and was calculated as the average of two withdrawal rate estimates for etanercept and infliximab. At the point of switching to the next treatment, patients were assumed to experience an increase in their HAQ score (rebound) equal to the initial HAQ improvement. After the initial 24-week period the HAQ score with tocilizumab plus methotrexate was assumed to decrease linearly (improve) based on the observational extensions to the RCTs. Because of substantial

uncertainty in the data for weeks 132–156, this continued improvement was only assumed for the first 3 years in the DMARD-IR cohort and 2.5 years in the TNF-IR cohort. After this (post-3 years after initial treatment in the DMARD-IR cohort and post-2.5 years after initial treatment in the TNF-IR cohort), the HAQ score was assumed to stay constant (that is, zero HAQ improvement) with tocilizumab plus methotrexate treatment. After the initial 24-week treatment period, no change in HAQ score was assumed (zero HAQ improvement) for biological treatments such as etanercept and rituximab. After the initial 24-week treatment period, an increase in HAQ score (that is, a worsening of physical function) was assumed for traditional DMARDs. The manufacturer also carried out sensitivity analyses using an assumption of zero HAQ progression (no improvement or worsening) while on treatment.

3.19 Tocilizumab plus methotrexate was assumed to be given for a minimum of 6 months and the administration cost of each infusion of tocilizumab was assumed to be £142 (see section 3.30 for subsequent considerations of administration costs). The costs of treating any adverse events were not included in the economic model presented by the manufacturer. The manufacturer reported that EQ-5D scores from the tocilizumab OPTION and LITHE trials were mapped to HAQ scores using a quadratic regression model. Alternative mapping equations as used in NICE technology appraisal guidance 130 and other submissions to NICE were examined in scenario analyses. Utility weights were derived from the EQ-5D scores using the UK time trade-off tariff. Adverse events associated with tocilizumab treatment were assumed to generate an insignificant burden in the quality of life of the patients, and therefore were not included in the model.

3.20 For the DMARD-IR population, the treatment sequence including tocilizumab plus methotrexate compared with the sequence without

tocilizumab produced incremental costs of £23,253 and incremental quality-adjusted life years (QALYs) of 1.17. This resulted in a base-case incremental cost-effectiveness ratio (ICER) of £19,870 per QALY gained. For the TNF-IR population, the treatment sequence including tocilizumab plus methotrexate compared with the sequence without tocilizumab produced incremental costs of £26,640 and incremental QALYs of 1.21. This resulted in a base-case ICER of £22,003 per QALY gained. Probabilistic sensitivity analyses suggested that the addition of tocilizumab and methotrexate to the treatment sequences had a 56.4% and 22.4% probability of being cost effective (for the DMARD-IR and TNF-IR populations respectively) if the maximum acceptable amount to pay for a QALY gained is £20,000. All scenario analyses presented by the manufacturer resulted in ICERs of less than £30,000 per QALY gained. The ICERs increased to £24,905 and £24,739 per QALY gained for the DMARD-IR and TNF-IR populations respectively, using an assumption of no change in HAQ score (that is, no continued improvement on tocilizumab after the initial ACR response).

Evidence Review Group comments

3.21 The ERG stated that the manufacturer's submission identified all relevant published studies of tocilizumab in a population appropriate for the decision problem and that critical appraisal of the included studies was reasonably thorough. The ERG commented that the general approach to the modelling framework chosen was appropriate to the decision problem and that the broad structural assumptions used in modelling were appropriate and similar to previous models used to evaluate the cost effectiveness of biological treatments.

3.22 The ERG highlighted the following key areas of concern with the manufacturer's submission.

- The inclusion of the studies and the pooling of the TNF-α inhibitors in the mixed treatment comparison.
- The long-term estimates of HAQ score.
- Mapping HAQ scores to EQ-5D to derive utility estimates for the economic model.
- The rebound effect on discontinuation (defined as an increase in a person's HAQ score when treatment is withdrawn).
- The non-inclusion of adverse events in the economic model.

3.23 The ERG explored the combined adjusted ACR response rates for TNF-α inhibitors used in the mixed treatment comparison (DMARD-IR population) and considered that etanercept appeared less efficacious in the comparison than the literature suggested. The ERG commented that the reason for the apparent low efficacy of etanercept compared with both tocilizumab and the other TNF-α inhibitors was a single large trial with a very high response rate in the placebo arm (the Klareskog trial). The ERG noted that this trial only included patients who were likely to benefit from methotrexate and had an aggressive dosing schedule of methotrexate if the signs and symptoms of rheumatoid arthritis reappeared. When the ERG removed the Klareskog trial from the analysis, etanercept appeared more efficacious than tocilizumab and all the other treatments in the comparison. The ERG then questioned the validity of assuming that all TNF-α inhibitors had the same efficacy in the model, because this lowered the estimate of the effectiveness of the TNF-α inhibitor used in the model. When the ERG investigated the use of unpooled parameters in the economic model for the DMARD-IR population (that is, the withdrawal rate of etanercept was reduced from 10% to 8%), the incremental costs were reduced to £22,887 and incremental QALYs were reduced to 1.13. This resulted in an increase in the DMARD-IR ICER from £19,870 to £20,166 per QALY gained.

3.24 The ERG commented that the follow-up period of 24 weeks in the five included tocilizumab studies could be considered too short. It noted that the longer-term data on tocilizumab came from single-arm studies with no comparator of placebo, conventional DMARDs or biological agents, so the long-term effectiveness of tocilizumab was unclear. The manufacturer estimated the medium-term HAQ progression (up to 3 years for the DMARD-IR population and 2.5 years for the TNF-IR population) using linear functions. However, the ERG suggested that an exponential function was equally plausible. The ERG noted that any functions fitted to the data needed to be constructed carefully because even small changes to the predictions would have a significant impact on the ICER.

3.25 The ERG was also concerned about the way the relationship between HAQ and EQ-5D was modelled. The manufacturer's submission used a quadratic equation for this. The quadratic model predicted that EQ-5D scores would be lower at high HAQ scores compared with a linear model. In addition, literature has shown that EQ-5D and HAQ are closely correlated at baseline and that when quality of life worsened over time the EQ-5D became more variable (resulting in a weaker correlation). The ERG noted that the modelled relationship between HAQ and EQ-5D scores resulted in negative utilities for health states (that is, health states that are considered to be worse than death). The ERG stated that using negative utility values is questionable because a certain amount of disability (due to irreversible characteristics such as damaged joints) may remain despite optimal control of inflammatory disease. The ERG concluded that algorithms for modelling the relationship between HAQ and EQ-5D should only be used when there are no direct utility scores; however, the trials for tocilizumab (OPTION and LITHE) measured EQ-5D directly. When the ERG removed negative EQ-5D utility scores from the model for the DMARD-IR population, the ICER increased from £19,870 to £20,214 per QALY

gained. The effect on the base-case ICER for the TNF-IR population was not modelled, but the ERG stated that it was likely to also be increased.

3.26 The manufacturer assumed the cost of administering each infusion of tocilizumab was £142. This was derived by adjusting for inflation the cost of an infusion as used in TA130. However, the ERG commented that this cost should have been adjusted for inflation from 2001 and not from 2004 as was presented by the manufacturer.

3.27 The manufacturer's submission assumed that the rebound after withdrawal from treatment was equal to the initial HAQ improvement only. The manufacturer's submission also assumed that the HAQ score for patients treated with tocilizumab improved over the course of treatment, but that for other treatments the HAQ score either remained the same (biological treatments) or worsened (conventional DMARDs and palliative care). Therefore, it was assumed that the short- to medium-term HAQ benefit was retained in the long term. TA130 accepted a similar assumption that patients would lose their initial HAQ improvement when treatment was withdrawn, and also that biological treatments delayed disease progression more than conventional DMARDs. However, whereas the HAQ score representing underlying disease progression for all biological treatments in TA130 remained the same or worsened only slightly while on treatment, the manufacturer assumed that HAQ score improvement was possible for tocilizumab only. The ERG commented that the assumptions about rebound effect and HAQ progression disproportionately favoured tocilizumab by not only allowing the drug to delay disease progression, but also by allowing for a lasting improvement of the condition. When the ERG investigated the use of a different rebound effect following withdrawal from treatment (as was used in the economic model for TA130) for the DMARD-IR population, the

incremental costs were unchanged from the base case and the incremental QALYs were reduced to 0.96. This resulted in the ICER increasing from £19,870 to £24,252 per QALY gained. Although not modelled, the ERG predicted that the respective ICERs for the TNF-IR population would be higher than the manufacturer's base case of £22,003 per QALY gained.

3.28 In addition, the ERG considered that excluding adverse events in the manufacturer's model was questionable because biological treatments are known to be associated with adverse events. The ERG noted that the manufacturer's submission compared the adverse events for tocilizumab with those of methotrexate. It reported that it was unclear whether the adverse event rate is higher or lower for tocilizumab than for other biological treatments. The manufacturer's submission states that the mean and median duration of treatment with tocilizumab in the clinical trials was 1.08 years. The ERG commented that the risks of longer-term treatment with tocilizumab were unknown. The ERG incorporated a QALY loss of 0.05 for every cycle that a person is on any DMARD treatment (except for palliative care) for the DMARD-IR population to estimate the effects of adverse events. The incremental costs were unchanged from the base case and the incremental QALYs were reduced to 0.94. This resulted in the ICER increasing from £19,870 to £24,629 per QALY gained. Although not modelled, the ERG predicted that the respective ICERs for the TNF-IR population would be higher than the manufacturer's base case of £22,003 per QALY gained.

3.29 The ERG also calculated the cumulative effect on the DMARD-IR ICER of combining some of the suggested changes. The ERG used unpooled parameters for estimating the withdrawal rate (detailed in section 3.23) with a rebound effect following withdrawal from treatment (detailed in section 3.27) and incorporated a disutility associated with the effects of adverse events (detailed in

section 3.28). The cumulative effect of these changes reduced the incremental costs to £22,910 and the incremental QALYs to 0.71. This resulted in the ICER increasing from £19,870 to £32,410 per QALY gained. Although not modelled, the ERG predicted that the respective cumulative ICERs for the TNF-IR population would be higher than the manufacturer's base case of £22,003 per QALY gained.

Manufacturer's response to consultation

3.30 In response to consultation, the manufacturer calculated the cumulative effect of combining some of the ERG's suggested changes on the DMARD-IR and TNF-IR ICERs. For the DMARD-IR population, the manufacturer used the same unpooled parameters for estimating the withdrawal rate as the ERG (detailed in section 3.23) and used unpooled parameters in the mixed treatment comparison. A rebound effect following withdrawal from treatment to baseline (detailed in section 3.27) and increased administration costs of £154 per infusion were incorporated. The cumulative effect of these changes resulted in the DMARD-IR ICER increasing from £19,870 to £23,655 per QALY gained. For the TNF-IR population, the manufacturer included a rebound effect following withdrawal from treatment to baseline (detailed in section 3.27) and increased administration costs of £154 per infusion were incorporated. The cumulative effect of these changes resulted in the TNF-IR ICER increasing from £22,003 to £23,318 per QALY gained.

3.31 In response to the Committee's requests made at the second Committee meeting, the manufacturer provided additional long-term tocilizumab HAQ data, EQ-5D data and safety data. Revised cost-effectiveness estimates were also presented for a number of scenarios, including two changes to the mixed treatment comparison, HAQ rebound to baseline, and slightly raised tocilizumab administration costs of £154. Individually, these

parameter changes increased the DMARD-IR ICER by £79 and £319, £2133 and £464 respectively. It was not relevant to apply the mixed treatment comparison changes to the TNF-IR ICER; however, the HAQ rebound to baseline and raised administration costs increased the TNF-IR ICER by £873 and £425 respectively. The manufacturer also provided a non-linear extrapolation of medium-term HAQ, which had not been requested by the Committee. This analysis used the mean HAQ scores for the patients who remained on tocilizumab treatment in the single-arm extension trials (1258 patients at week 24 which decreased to 888 patients at week 168 in the DMARD-IR population, and 155 patients at week 24 which decreased to 96 patients at week 132 in the TNF-IR population). This change decreased the DMARD-IR ICER by £1166 and the TNF-IR ICER by £2525. The cumulative effect of all the changes (that is, the increases and reductions) resulted in the ICER increasing from £19,870 to £22,994 per QALY gained for the DMARD-IR population. The cumulative effect of the parameter changes resulted in the TNF-IR ICER increasing from £22,003 to £23,318 per QALY gained.

3.32 In response to the Committee's requests made at the third Committee meeting, the manufacturer provided revised ICERs for the DMARD-IR and TNF-IR populations. The manufacturer also provided ICERs for the two positions for which the Committee had requested further information, that is, tocilizumab used after an inadequate response to rituximab, and tocilizumab for patients who are intolerant to rituximab or for whom rituximab is contraindicated. The clinical-effectiveness data for tocilizumab used in these positions were taken from the RADIATE trial. All of the revised and new ICERs incorporated degraded ACR response rates for tocilizumab, etanercept and rituximab when they are used later in the treatment sequence. Estimates for etanercept were based on treatment response to a second or third TNF-α inhibitor reported from the South Swedish Arthritis Treatment Group. These

downgraded the efficacy of etanercept from 62%, 38% and 16% to 49%, 26% and 7% for ACR20, ACR50 and ACR70 response rates respectively when used after one biological treatment. For tocilizumab when used after two biological treatments, degraded rates were based on the subgroup of patients from the RADIATE trial whose rheumatoid arthritis had responded inadequately to more than one TNF-α inhibitor. Based on these data, tocilizumab response rates were downgraded from 62%, 31% and 12% to 50%, 31% and 15% for ACR20, ACR50 and ACR70 response rates respectively. For rituximab used after two biological treatments, the manufacturer provided downgraded response rates based on a subgroup of patients whose rheumatoid arthritis had responded inadequately to more than one TNF-α inhibitor from a trial comparing rituximab plus methotrexate with placebo plus methotrexate (REFLEX). Based on these data, the rituximab response rates were downgraded from 46%, 23% and 14% to 42%, 22% and 10% respectively.

3.33 The revised ICERs were based on the adjusted ACR rates from the mixed treatment comparison, and included a long-term HAQ improvement for tocilizumab and a stable HAQ score (that is, zero HAQ progression) for all other biological treatments. This was not the case for the ICER for tocilizumab given after rituximab, for which no HAQ improvement for treatment with any biological treatment, including tocilizumab, was assumed. All of the revised ICERs were calculated using the HAQ to EQ-5D mapping and included negative utilities that represented states worse than death. The ICERs were subject to the assumption that a person would experience the same adverse events during treatment as during palliative care, and that the cost of administration of tocilizumab was £154.

3.34 The manufacturer's revised ICER for the DMARD-IR population decreased from £22,994 to £21,733 per QALY gained and

decreased from £23,318 to £23,285 per QALY gained for the TNF-IR population. The ICER for tocilizumab used after rituximab was £23,735 per QALY gained. The ICER for tocilizumab for patients who are intolerant of rituximab or for whom rituximab is contraindicated was £20,242 per QALY gained.

Report by the Decision Support Unit

3.35 After the third Committee meeting, the Decision Support Unit (DSU) was asked to undertake additional cost-effectiveness analyses to validate the manufacturer's ICERs, and to conduct sensitivity analyses to address the Appraisal Committee's concerns about key parameter assumptions. The report highlighted a key issue with the calculation of the ICERs presented by the manufacturer. This concerned the 'pair-wise' calculation of sequences containing tocilizumab plus methotrexate with the same sequence excluding tocilizumab rather than an 'incremental' comparison of all strategies containing tocilizumab plus methotrexate with each other and with a base-case strategy without tocilizumab. The DSU stated that the incremental approach was the most appropriate, not only to determine whether tocilizumab plus methotrexate was cost effective, but also in what circumstances, given the availability of a number of other treatments that are used sequentially. The DSU report explained that an ICER calculated through a pair-wise comparison does not demonstrate that the sequence can be considered cost effective as there are a series of mutually exclusive sequences available and only one can be selected at any one time. Only a fully incremental analysis that ranks the alternative sequences in ascending order of costs or effects can determine the true cost-effectiveness estimates for any of the treatment sequences.

3.36 For etanercept, the mixed treatment comparison analysis combined all TNF-α inhibitors (etanercept, infliximab and adalimumab) but excluded the Klareskog trial of etanercept that the Committee had

requested to be removed because of the unusually high placebo response rate in this trial. The DSU noted that the adjusted mixed treatment comparison rates were lower than the unadjusted trial ACR, or point estimate, rates for etanercept. The adjusted etanercept ACR20, ACR50 and ACR70 response rates were 62%, 38% and 16% respectively and the unadjusted ACR20, ACR50 and ACR70 response rates were 71%, 39% and 17% respectively. The DSU noted that the unadjusted rates in the model were taken from a single etanercept trial, without justification for the sole use of this particular trial. The DSU provided an alternative set of unadjusted response rates for etanercept, which were based on the two etanercept trials from the mixed treatment comparison (rather than the single trial chosen by the manufacturer). The DSU stated that this appeared to represent the most robust data. The resulting unadjusted ACR response rates were 73%, 47% and 22% for ACR20, ACR50 and ACR70 respectively. For rituximab, the adjusted mixed treatment comparison ACR response rates were also lower than the unadjusted ACR trial response rates. The percentage of people reaching an ACR20, ACR50 and ACR70 response rate was 51%, 27% and 12% respectively in the unadjusted analysis and 46%, 23% and 14% respectively in the adjusted analysis. The unadjusted data were taken from the REFLEX trial.

3.37 The DSU highlighted that the opposite effect was observed with the adjusted and unadjusted ACR rates for tocilizumab, that is, the adjusted rates from the mixed treatment comparison were higher than the unadjusted rates. For tocilizumab given as the first biological treatment in the sequence, the adjusted rates were 63%, 41% and 26% for ACR20, ACR50 and ACR70 response rates respectively and the unadjusted rates for tocilizumab, which were based on a separate meta-analysis of OPTION, TOWARD and LITHE (submitted as part of the manufacturer's licence application), were 59%, 37% and 19% respectively. For tocilizumab used as the

second biological treatment in a sequence (that is, after a TNF-α inhibitor), the mixed treatment comparison had the same effect of increasing the tocilizumab ACR response rates. The adjusted rates were 62%, 31% and 12%, whereas the unadjusted rates were 50%, 29% and 12% for ACR20, ACR50 and ACR70 response rates respectively. The unadjusted rates for tocilizumab used as the second biological treatment in the sequence were taken from the RADIATE trial.

3.38 The DSU also commented on the degradation rates provided by the manufacturer in response to the consultation after the third Committee meeting. These rates were all from single data sources, without justification given for the selection of the sources. The DSU highlighted that the degraded response rates for etanercept were based on the reported ACR rates for the TNF-α inhibitors as a group and may not have been generalisable to etanercept. The DSU also noted that the degraded ACR70 response rate for tocilizumab used after two biological treatments assumed by the manufacturer (15%) was marginally better than when used after a single biological treatment (12%). The DSU stated that this appeared to be counter-intuitive and that it would be more appropriate to assume the same ACR70 response rate when tocilizumab is given after two biological treatments as for when it is given after one.

3.39 The DSU therefore considered four separate approaches that varied the ACR response rates and degradation rates used to calculate the incremental ICERs (approaches to evidence synthesis).

- Approach 1 was the same as the manufacturer's revised base case and used the adjusted mixed treatment comparison results with the degradation rates supplied by the manufacturer.
- Approach 2 used the unadjusted single trial ACR response rates for etanercept when used first in the treatment sequence as

supplied by the manufacturer. All other estimates remained the same as in approach 1.

- Approach 3 used the unadjusted trial ACR response rates for all treatments in the sequence as supplied by the manufacturer. In addition, this approach replaced the degraded effect for tocilizumab when used after two biological treatments with the same effect assumed after one biological treatment to account for the counter-intuitive change in response rate assumed by the manufacturer (see section 3.38).
- Approach 4 was the same as approach 3, except that the DSU used the alternative unadjusted ACR response rates for etanercept from the two trials (described in section 3.36).

3.40 For each of the four approaches to evidence synthesis, the DSU undertook four sets of sensitivity analyses to assess the robustness of the ICER results to other key parameter assumptions. These were:

- employing the same set of parameter assumptions employed by the manufacturer in its base case
- assuming no long-term HAQ improvement with tocilizumab
- assuming no long-term HAQ improvement with tocilizumab and excluding negative utilities from the HAQ to EQ-5D mapping
- assuming no long-term HAQ improvement with tocilizumab and doubling the administration costs for tocilizumab to £308.60 per infusion.

3.41 The DSU calculated the incremental ICERs for each approach using the four sensitivity analyses and presented the incremental results separately for each of the 16 possible analyses. In each incremental analysis, the treatment strategies compared with each other were:

- etanercept followed by rituximab (strategy 1)

- tocilizumab plus methotrexate, followed by etanercept, followed by rituximab (strategy 2)
- etanercept, followed by tocilizumab plus methotrexate, followed by rituximab (strategy 3)
- etanercept, followed by rituximab, followed by tocilizumab plus methotrexate (strategy 4).

For all treatment strategies, the calculation of the ICER included the costs and QALYs associated with treatment with conventional DMARDs and palliative care at the end of the sequence.

3.42 For approach 1 with the manufacturer's base-case parameter assumptions (that is, the analysis reflecting that of the manufacturer's revised base case) and assuming a willingness to pay of £30,000 per QALY gained, the most cost-effective treatment strategy was strategy 3 (that is, tocilizumab plus methotrexate before rituximab in the treatment pathway). The ICER for this strategy was £27,310 per QALY gained. However, if the parameter assumptions were varied by assuming no long-term HAQ improvement with tocilizumab, the ICER with strategy 3 increased from £27,310 to £60,771 per QALY gained. When no long-term HAQ improvement was assumed for tocilizumab, the most cost-effective sequence was strategy 4 (that is, etanercept, then rituximab, then tocilizumab) with an ICER of £25,244 per QALY gained. By varying the third parameter assumption (that is, also excluding the negative utilities created by the manufacturer's HAQ to EQ-5D mapping), the most cost-effective treatment strategy was also strategy 4 with an ICER of £25,755 per QALY gained. By employing the fourth parameter assumption (that is, no HAQ improvement with tocilizumab and doubling the administration costs of tocilizumab from £154 to £308), the resulting ICERs for all strategies were all greater than £30,000 per QALY gained. The incremental costs for the ICERs calculated in approach 1 ranged

from £17,429 to £21,459 and the incremental QALYs ranged from 0.677 to 0.691.

3.43 For the three remaining approaches in which the ACR response rates and degradation rates were varied by the DSU, the most cost-effective strategy when the manufacturer's base-case parameters were used was always strategy 3. The ICERs for this strategy with all four approaches with the manufacturer's base-case assumptions ranged between £26,344 and £29,522 per QALY gained. However, when no long-term HAQ improvement was assumed, then the most cost-effective treatment strategy for all four approaches was strategy 4 (that is, etanercept, then rituximab, then tocilizumab) with ICERs of £25,568, £27,621 and £27,121 per QALY gained (with approaches 2, 3 and 4 respectively). When negative utility values were excluded (and no long-term HAQ improvement with tocilizumab assumed), then the most cost-effective strategy for all approaches was also strategy 4 (that is, tocilizumab used after rituximab) with ICERs of £26,041, £28,090 and £27,569 per QALY gained (with approaches 2, 3 and 4 respectively). By doubling the administration cost of tocilizumab (and no long-term HAQ improvement with tocilizumab), there were no ICERs that were cost effective with a willingness to pay of £30,000 per QALY gained. In this scenario, the most cost-effective strategy for all four approaches was strategy 1, the comparator sequence (that is, the strategy that does not contain tocilizumab: etanercept followed by rituximab). In approach 2, the incremental costs ranged from £17,072 to £20,988 and the incremental QALYs ranged from 0.656 to 0.668. In approach 3, the incremental costs ranged from £16,411 to £20,174 and incremental QALYs ranged from 0.592 to 0.602. In approach 4, the incremental costs ranged from £16,564 to £20,113 and the incremental QALYs ranged from 0.601 to 0.611. Probabilistic sensitivity analysis was not presented for the estimates of cost effectiveness.

3.44 The DSU undertook a separate analysis of tocilizumab used in place of rituximab for patients who have an intolerance to rituximab, or for whom rituximab is contraindicated. In this analysis, only two strategies were compared. The comparator sequence was etanercept followed by traditional DMARDs and palliative care, and the intervention sequence was etanercept followed by tocilizumab plus methotrexate. From the four approaches to evidence synthesis identified by the DSU (section 3.39), approach 2 was not relevant because this approach only made adjustments to the effects of etanercept and therefore would have no impact on this analysis, which would have been given earlier in the sequence. The remaining three approaches were combined with the variations to the parameter assumptions (as described in section 3.40). As with the results for the full population, the most cost-effective strategy did not differ according to the approach to evidence synthesis used. When the first three sets of parameter assumptions were employed (that is, the manufacturer's parameters, no long-term HAQ improvement with tocilizumab and negative utility values excluded), the sequence including tocilizumab was always cost effective at a willingness to pay of £30,000 per QALY gained. When the manufacturer's parameters were used, the ICERs were £21,196, £23,370 and £23,342 per QALY gained (with approaches 1, 3 and 4 respectively). The incremental costs ranged from £17,972 to £22,770 and incremental QALYs from 0.769 to 1.075. When no long-term HAQ improvement was assumed, then the ICERs were £25,105, £27,950 and £27,917 per QALY gained (with approaches 1, 3 and 4 respectively). The incremental costs ranged from £17,972 to £22,778 and incremental QALYs from 0.643 to 0.907. When the negative utility values were excluded and no long-term HAQ improvement was assumed, then the ICERs were £25,619, £28,428 and £28,392 per QALY gained (with approaches 1, 3 and 4 respectively). The incremental costs ranged from £17,972 to £22,770 and incremental QALYs from 0.633 to 0.889. However, when the administration cost of tocilizumab was

doubled the resulting ICERs for all approaches were greater than £30,000 per QALY gained. Probabilistic sensitivity analysis was not presented for the estimates of cost effectiveness.

3.45 In summary, at a willingness to pay of £30,000 per QALY gained, the results of the fully incremental analysis undertaken by the DSU indicated that using tocilizumab plus methotrexate as a first-line treatment before etanercept is never cost effective for any approach and with any set of parameter assumptions (including the manufacturer's base-case assumptions). Using tocilizumab plus methotrexate as a second-line treatment before rituximab is only cost effective if it is assumed that tocilizumab has long-term HAQ improvement and there is no HAQ improvement assumed with other biological treatments. However, if tocilizumab has zero HAQ improvement, then tocilizumab plus methotrexate is only cost effective when used as a third-line treatment after rituximab. If tocilizumab has zero HAQ improvement and the administration costs of tocilizumab are doubled, then tocilizumab plus methotrexate is never cost effective (that is, standard care is the most cost-effective sequence). For patients who have an intolerance to rituximab, or for whom rituximab is contraindicated, adding tocilizumab to the current standard care is cost effective. However, if tocilizumab does not have a different effect on long-term HAQ and the administration costs of tocilizumab are doubled, then the current standard care is also more cost effective for this population.

3.46 Full details of all the evidence are in the manufacturer's submission, the ERG report, and the report from the DSU, which are available from www.nice.org.uk/guidance/TA198

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 rheumatoid arthritis 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 first discussed tocilizumab given as monotherapy. It noted that the only clinical evidence for tocilizumab monotherapy came from a trial that included people who had not been previously treated with methotrexate and that tocilizumab monotherapy treatment for this population was outside the licensed indication of tocilizumab. The Committee also noted that no cost-effectiveness estimates of tocilizumab given as monotherapy had been presented by the manufacturer. It concluded that no evidence for tocilizumab monotherapy within its licensed indication was available, and therefore no recommendations for tocilizumab as a monotherapy could be made.

4.3 The Committee understood that the main purpose of treatment for rheumatoid arthritis is to suppress inflammation, which in turn can slow disease progression and prevent irreversible joint damage. The Committee heard from the clinical specialists and patient experts that the primary concern with tocilizumab treatment was the potential for infectious complications, but that trial data suggested that most adverse events were relatively minor, and, in most cases, did not limit treatment use. The Committee noted the updated safety data presented by the manufacturer, which reported 27 deaths and a serious adverse event rate of 5.8%. The Committee considered that this adverse event rate was high, but heard that it was comparable with other biological treatments.

4.4 The Committee discussed the treatment options for people with moderate to severe active rheumatoid arthritis. It understood that NICE technology appraisal guidance 130 recommended the use of TNF-α inhibitors adalimumab, etanercept and infliximab as options for the treatment of adults whose rheumatoid arthritis has responded inadequately to two DMARDs (unless DMARDs are contraindicated). Treatment with rituximab plus methotrexate is recommended if there has been an inadequate response to DMARDs including at least one TNF-α inhibitor (NICE technology appraisal guidance 126). The Committee was aware that following an inadequate response to rituximab, additional DMARDs and best supportive care would be offered. The Committee understood that the manufacturer presented evidence for tocilizumab as an additional treatment before TNF-α inhibitors (defined by the manufacturer as DMARD-IR) and before rituximab (defined by the manufacturer as TNF-IR). However, the Committee did not consider that this represented the full range of possible options for treatment with tocilizumab. It was aware of clinical specialist and patient expert opinion that there is a need for an additional treatment option after an inadequate response to treatment with rituximab or when rituximab is contraindicated. The Committee considered that there were six possible scenarios for including tocilizumab in the treatment pathway:

- Tocilizumab after two DMARDs as an alternative to TNF-α inhibitors.
- Tocilizumab after TNF-α inhibitors as an alternative to rituximab.
- Tocilizumab as an additional treatment in the pathway after two DMARDs and before TNF-α inhibitors.
- Tocilizumab as an additional treatment in the pathway after TNF-α inhibitors and before rituximab.
- Tocilizumab after TNF-α inhibitors when a person is intolerant to rituximab or for whom rituximab is contraindicated.

- Tocilizumab as an addition to the treatment pathway after rituximab.

Clinical effectiveness

4.5 The Committee considered the evidence on the clinical effectiveness of tocilizumab plus DMARDs compared with placebo plus DMARDs. The Committee noted that there were statistically significant improvements with tocilizumab plus DMARDs (mainly methotrexate) compared with DMARDs plus placebo for both the DMARD-IR and TNF-IR populations. The Committee noted that there were also improvements in HAQ and DAS28 scores in the three RCTs of people receiving tocilizumab plus DMARDs in the DMARD-IR population. The Committee therefore concluded that tocilizumab plus methotrexate was clinically effective compared with placebo plus DMARDs when given before TNF-α inhibitors and when given before rituximab.

4.6 The Committee then considered whether tocilizumab had been shown to be superior to etanercept and rituximab by the DMARD-IR and the TNF-IR data respectively. It understood that tocilizumab had not been compared head-to-head with either etanercept (or any other TNF-α inhibitor) or rituximab and that indirect evidence had been combined in a mixed treatment comparison for this purpose. It noted the concerns raised by the ERG and clinical specialists regarding the mixed treatment comparison. The mixed treatment comparison assumed that the TNF-α results could be regarded as a class; however, when merged, the overall results reduced the efficacy of etanercept. The Committee noted that the manufacturer had responded to requests to remove the Klareskog trial of etanercept from the analysis because this was a large RCT with unusually high control-arm response rates and did not correspond with the inclusion criteria of the mixed treatment comparison. With this trial removed, the Committee noted that etanercept appeared at least equal to, and

possibly had higher efficacy than, tocilizumab. Therefore the Committee concluded that the results of the mixed treatment comparison should be viewed with caution.

4.7 The Committee further examined the results of the mixed treatment comparison. It noted the concerns of the DSU regarding the adjusted ACR response rates from the mixed treatment comparison compared with the 'unadjusted' point estimates from the individual trials. It understood that the proportions of people achieving ACR20, ACR50 and ACR70 response rates for etanercept and rituximab resulting from the mixed treatment comparison were lower than the corresponding unadjusted trial ACR response rates. Conversely, the proportions of people achieving ACR20, ACR50 and ACR70 response rates were higher for tocilizumab in the adjusted mixed treatment comparison analysis than the unadjusted trial rates. The DSU clarified that the counter-intuitive results of the mixed treatment comparison had possibly arisen when the comparator response rates from all of the trials had been pooled. The DSU further advised that the results of a mixed treatment comparison are dependent on the selection of trials that inform the analysis and that the response rates of the trials informing the mixed treatment comparison should have been more closely considered by the manufacturer. The Committee considered that the mixed treatment comparison included a set of heterogeneous trials, which meant that the results were subject to considerable uncertainty, and that limited confidence could be placed in the adjusted ACR response rates in the manufacturer's revised base case. The Committee agreed that using the unadjusted trial estimates in the analyses, in this instance, was more appropriate. Therefore, based on the unadjusted trial estimates, the Committee concluded that an additional clinical benefit of tocilizumab over etanercept or rituximab had not been demonstrated.

4.8 The Committee noted comments from clinical specialists and patient experts received in response to consultations that tocilizumab has a different mode of action to other biological treatments, which may offer a benefit for patients who have not experienced a response with two biological treatments. It also acknowledged the manufacturer's argument that three biological treatments may offer the potential for delaying disease progression for longer than two biological treatments. The Committee considered that, although the superiority of tocilizumab compared with etanercept or rituximab had not been demonstrated, it may be clinically effective after treatment with rituximab. The Committee considered the clinical evidence for tocilizumab in this position. Based on previous discussions it recognised that tocilizumab plus methotrexate is clinically effective compared with placebo plus methotrexate (see section 4.5). It noted the evidence from the RADIATE trial in which a subgroup of people had rheumatoid arthritis that had responded inadequately to two TNF-α inhibitors. It understood that this was the only available evidence to consider the effectiveness of tocilizumab after rituximab. The Committee considered that it indicated a benefit of tocilizumab after two biological treatments. In view of this evidence and considering the comments from patient experts and clinical specialists, the Committee, on balance, agreed that tocilizumab was likely to be clinically beneficial for people with moderate to severe active rheumatoid arthritis whose rheumatoid arthritis has responded inadequately to rituximab.

Cost effectiveness

4.9 The Committee discussed the cost-effectiveness estimates presented by the manufacturer in which tocilizumab was considered as an additional treatment in four positions in the pathway: before etanercept, before rituximab, after rituximab and when rituximab is contraindicated. It noted that the cost of etanercept was similar to tocilizumab, although etanercept is given

as a subcutaneous injection and therefore incurs lower administration and monitoring costs than tocilizumab. It further noted that the cost of rituximab is approximately half of the cost of tocilizumab. Having already concluded on the basis of the clinical evidence that the superiority of tocilizumab in comparison with etanercept or rituximab had not been demonstrated, the Committee was not persuaded that tocilizumab, when used as an alternative to etanercept or rituximab, would represent a cost-effective use of NHS resources. The Committee agreed that it would not be logical to recommend a treatment before one that was more cost effective. In addition, the Committee noted that the manufacturer's estimates of cost effectiveness had been calculated using pair-wise comparisons of individual sequences with and without tocilizumab. The Committee noted the DSU report, which clarified that in order to estimate the cost effectiveness of tocilizumab, each treatment sequence should have been calculated incrementally. The Committee understood that the incremental approach compared all of the possible positions of tocilizumab in the treatment pathway and a strategy without tocilizumab simultaneously. The DSU reiterated that this was the only valid approach because the possible treatment pathways were mutually exclusive (that is, only one pathway could be followed by each patient). The Committee accepted that an incremental analysis was an appropriate method to assess the cost effectiveness of tocilizumab.

4.10 The Committee discussed the incremental analysis by the DSU in which four approaches to evidence synthesis (see section 3.39) were presented. The Committee considered on the basis of previous discussions (see section 4.7) that approach 1, in which the ACR response rates came from the mixed treatment comparison, was not appropriate. The Committee therefore discussed the remaining three approaches to evidence synthesis, which used the unadjusted trial response rates for all treatments and incorporated degradation rates. It understood that

approaches 2 and 3 only used the unadjusted ACR response rate from a single trial for etanercept, rather than from the two available trials. The Committee had a strong preference for approach 4, which used data from both of the etanercept trials. Approach 4 also corrected the counter-intuitive ACR70 response rate for tocilizumab used as a third biological treatment in the treatment sequence noted by the DSU. The Committee concluded that the incremental ICERs derived using approach 4 to evidence synthesis (see section 3.39) were the most appropriate for consideration.

4.11 The Committee discussed the evidence supplied by the manufacturer for a long-term HAQ improvement. It understood that the data for a HAQ improvement with tocilizumab treatment came from open-label extension studies in which only the HAQ scores for those patients who remained on treatment were available. It noted that, for the open-label extension trial assessing the benefits of tocilizumab after the failure of conventional DMARDs (that is, before etanercept), approximately 30% of patients had stopped treatment. It further noted that the confidence intervals around the mean HAQ scores at each point in time were wide. The Committee therefore considered that the manufacturer's evidence was not a robust estimation of the long-term HAQ improvement on tocilizumab and was subject to uncertainty. Furthermore, the manufacturer had not provided any comparable investigation into long-term HAQ trends for the comparator biological treatments other than rituximab. The manufacturer presented a graph of a stable HAQ trend for patients on rituximab from the REFLEX trial. However, no data had been supplied by the manufacturer to support the graph. The Committee questioned the comparability of the rituximab and tocilizumab HAQ trend lines, and considered that single-arm extension trial data did not provide a direct comparison of the relative benefits between the two treatments. In addition, the Committee heard from patient experts and clinical specialists that it was unlikely that tocilizumab would provide a long-term HAQ

benefit over and above that of any other biological treatment. Overall, the Committee could not support the assumption that there is a long-term HAQ gain with tocilizumab (that is, a HAQ improvement with tocilizumab) compared with no HAQ improvement with other biological treatments. It concluded, on the basis of the evidence presented, that the long-term HAQ improvement on tocilizumab treatment had not been demonstrated. The Committee agreed that the analyses that assumed no long-term HAQ improvement with tocilizumab were therefore the most appropriate for consideration.

4.12 The Committee considered the exclusion of negative utilities from the incremental analysis. The Committee noted that the manufacturer's mapping of HAQ scores to EQ-5D utility values resulted in states worse than death. It discussed that this could be considered counter-intuitive and did not allow for a worsening of quality of life when a person had rheumatoid arthritis. The Committee heard from the manufacturer that it was possible that there were some people with rheumatoid arthritis who may experience negative utility values. The Committee noted that the impact of removing the negative utilities from the incremental analysis was minimal. The Committee agreed that although the exclusion of negative utility values was subject to some debate, it was not a key issue in determining the cost effectiveness of tocilizumab. The Committee therefore considered that the ICERs from the incremental analysis in which the negative utility values were included were acceptable.

4.13 The Committee considered the administration costs of tocilizumab. It noted comments received during consultation that, although the infusion was 1 hour, the total time taken to administer tocilizumab in an organised unit would be at least 2 hours. The Committee then discussed the DSU analysis using approach 4 with no long-term HAQ improvement and the administration costs doubled. It heard

from the DSU that the decision to double the cost was not based on a robust estimate of the time taken to administer tocilizumab, but was intended to illustrate the sensitivity of the ICERs to this assumption. Although the Committee agreed that a cost based on an administration time of 1 hour represented the minimum cost to the NHS, it did not agree that the true cost would be as much as double. The Committee therefore considered that the ICERs from the incremental analysis in which the administration cost of tocilizumab had been doubled were not appropriate and concluded that the manufacturer's revised estimate of £154 was acceptable.

4.14 The Committee noted that some modelling assumptions in the manufacturer's submission had not been investigated by the DSU. These included, first, that none of the incremental ICERs assumed any difference in the adverse events that may occur on biological treatment compared with those that might occur in palliative care. Second, that despite previous requests to the manufacturer to use directly observed EQ-5D data, the revised base-case ICERs from the manufacturer were still subject to a HAQ mapping algorithm. The Committee highlighted its concern with this, but acknowledged that the data had not been available to investigate these assumptions.

4.15 The Committee therefore considered the ICERs from the incremental analysis based on approach 4 to evidence synthesis in which the ACR response rates came from the trials rather than the mixed treatment comparison and used a corrected degradation factor for tocilizumab (see section 3.39). From the results presented for this approach, the Committee agreed on those calculated using the second sensitivity analysis that assumed no long-term HAQ improvements with tocilizumab. The Committee noted that at a willingness to pay threshold of £30,000 per QALY gained, the only strategy that was cost effective was that of tocilizumab plus methotrexate given after rituximab. The

incremental ICER for tocilizumab plus methotrexate in this position in the treatment sequence was £27,100 per QALY gained. This was based on incremental costs of approximately £16,600 and approximately 0.6 incremental QALYs gained. The remaining two strategies containing tocilizumab were either extendedly dominated by a combination of two more cost-effective strategies (when tocilizumab is before etanercept in the treatment pathway) or had a much higher incremental ICER (when tocilizumab is before rituximab in the treatment pathway). The Committee concluded that tocilizumab, in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in people whose rheumatoid arthritis has responded inadequately to one or more TNF-α inhibitors and whose rheumatoid arthritis has also responded inadequately to rituximab, represented a cost-effective use of NHS resources.

4.16 The Committee discussed the cost effectiveness of tocilizumab plus methotrexate after TNF-α inhibitors when a person is intolerant of rituximab or for whom rituximab is contraindicated. It first considered the definition of intolerance to rituximab. It considered that, in general, if intolerance occurred during treatment with rituximab, this would constitute an inadequate response and therefore the recommendation previously discussed (see section 4.15) would apply. The Committee was aware from clinical specialists that rituximab may be associated with lower effectiveness in people with seronegative rheumatoid arthritis. However, as there are no specific recommendations in NICE technology appraisal 126 for rituximab according to seronegative status, this subgroup would have the option to receive rituximab and the recommendation previously discussed (see section 4.15) would apply.

4.17 The Committee explored whether there were people who were unable to receive rituximab because of a specific disability or

comorbidity. The Committee noted that no such group of people had been identified during scoping or in consultation. In addition, the mode of administration of rituximab was by infusion and fewer infusions per year were needed than with tocilizumab treatment. Therefore, the Committee considered that there were no groups of people who would not receive rituximab because of additional disabilities or comorbidity and for whom tocilizumab would be more suitable. The Committee agreed that, in general, it was only people with contraindications to rituximab who would not have the option to try rituximab treatment before tocilizumab. The Committee noted however that there may be a subgroup of patients who may have been able to try rituximab treatment, but who had rituximab withdrawn due to adverse events, rather than intolerance. It considered that the analysis conducted by the DSU of tocilizumab used in place of rituximab for patients who have an intolerance to rituximab, or for whom rituximab is contraindicated was also relevant to this subgroup of patients. The Committee therefore discussed the DSU analysis. It considered that the same conclusions about the sensitivity analysis parameters were applicable to the decision for this subgroup of patients. That is, the Committee did not accept a long-term HAQ improvement for tocilizumab alone, but accepted the inclusion of negative utilities and an administration cost of £154. The resulting ICER using these assumptions for people in whom rituximab is contraindicated or who have rituximab withdrawn due to adverse events was £27,900 per QALY gained. This was based on incremental costs of approximately £18,000 and approximately 0.6 incremental QALYs gained. The Committee concluded that tocilizumab plus methotrexate, for people whose rheumatoid arthritis has responded inadequately to previous treatment with a TNF-α inhibitor and for whom rituximab is contraindicated or who had rituximab withdrawn due to adverse events, represented a cost-effective use of NHS resources.

Summary

4.18 For people whose rheumatoid arthritis has responded inadequately to one or more previous DMARDs, tocilizumab plus methotrexate is not recommended for the treatment of moderate to severe active rheumatoid arthritis before, or as an alternative to, treatment with TNF-α inhibitors. For people whose rheumatoid arthritis has responded inadequately to one or more previous TNF-α inhibitors, tocilizumab plus methotrexate is not recommended for the treatment of moderate to severe active rheumatoid arthritis before, or as an alternative to, treatment with rituximab. The Committee concluded that tocilizumab as monotherapy could also not be recommended as a cost-effective use of NHS resources. However, the Committee recommended tocilizumab plus methotrexate as an option for people whose rheumatoid arthritis has responded inadequately to treatment with one or more previous TNF-α inhibitors and rituximab. The Committee also recommended tocilizumab plus methotrexate as an option for people with moderate to severe active rheumatoid arthritis whose rheumatoid arthritis has responded inadequately to one or more previous TNF-α inhibitors and in whom rituximab is contraindicated or who had rituximab withdrawn because of an adverse event.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS 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 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA198).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee suggested that a head-to-head trial of tocilizumab compared with rituximab would be useful.

7 Related NICE guidance

Published

- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 195 (2010). Available from www.nice.org.uk/guidance/TA195
- Certolizumab pegol for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 186 (2010). Available from www.nice.org.uk/guidance/TA186
- Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline 79 (2009). Available from www.nice.org.uk/guidance/CG79
- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007). Available from www.nice.org.uk/guidance/TA130

8 Review of guidance

8.1 The guidance on this technology will be considered for review in June 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
August 2010

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.

Dr David Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden
Consultant in Intensive Care Medicine/Anaesthesia Sheffield Teaching Hospitals NHS Trust

Professor Mike Campbell
Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler
Lay member

Dr Chris Cooper
General Practitioner, St John's Way Medical Centre, London

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Stephen Greep

Chief Executive of Hull and East Yorkshire Hospitals NHS Trust

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital London

Professor Gary McVeigh (Vice Chair)

Cardiovascular Medicine, Queen's University Belfast and Consultant Physician Belfast City Hospital

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Neil Myers

General Practitioner

Dr Richard Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay member

Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

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

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

Paul Trueman
Health Economics Research Group, Brunel University

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.

Joanne Holden
Technical Lead

Rebecca Trowman
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 West Midlands Health Technology Assessment Collaboration:

- Meads C et al., Tocilizumab for the treatment of rheumatoid arthritis, April 2009

B The Decision Support Unit report for this appraisal was prepared by the Centre for Health Economics, University of York:

- Palmer S, Sculpher M. Tocilizumab for the treatment of rheumatoid arthritis, May 2010

C 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 gave their expert views on tocilizumab by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Roche Products (tocilizumab)

II Professional/specialist and patient/carer groups:

- Arthritis & Musculoskeletal Alliance (ARMA)
- Arthritis Care
- National Rheumatoid Arthritis Society
- British Health Professionals in Rheumatology
- British Society for Rheumatology
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Abbott Laboratories (adalimumab)
- AstraZeneca UK (chloroquine)
- GlaxoSmithKline (azathioprine)
- Novartis (ciclosporin)
- Pfizer (methotrexate, sulfasalazine)
- Roche Products (rituximab)
- Sanofi-aventis (hydroxychloquine, leflunomide, sodium aurothiomalate)
- Schering-Plough (infliximab)
- Wyeth Pharmaceuticals (etanercept)
- West Midlands Health Technology Assessment Collaboration
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)

D 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 rheumatoid arthritis by attending the initial Committee discussion and providing written evidence to the Committee. They were invited to comment on the ACD.

- Dr Pavaladurai Vijayadurai, Consultant Immunologist, nominated by Royal College of Pathologists – clinical specialist
- Professor Peter C Taylor, Professor of Experimental Rheumatology and Honorary Consultant Rheumatologist, nominated by The British Society for Rheumatology – clinical specialist
- Dr Andrew J K Oster, Consultant Rheumatologist & Associate Lecturer, School of Clinical Medicine, University of Cambridge, Director, Rheumatology Clinical Research Unit, nominated by The British Society for Rheumatology – clinical specialist

- Ailsa Bosworth, Chief Executive, National Rheumatoid Arthritis Society (NRAS), nominated by NRAS – patient expert
- Jean Burke, Management Consultant, Comma Consulting, nominated by NRAS – patient expert

E 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