NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide the following:

- Justification for excluding some of the comparators and outcomes listed in the scope
- American College of Rheumatology criteria 70 (ACR70) data for golimumab and the comparators
- Further details of the adverse event data
- Clarification of the search strategy used in the systematic review
- Further details of one of the golimumab trials
- Justification for some of the assumptions used in the model.

Licensed indication

Golimumab (Simponi, Schering Plough), in combination with methotrexate, is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including methotrexate has been inadequate. Golimumab has also been shown to improve physical function in this patient population.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission includes comparator interventions for which there was positive NICE guidance at the time of submission. However, since the submission was made NICE has published guidance for other treatments that could be considered comparators for golimumab. Does the Committee consider that the comparators included in the submission are appropriate?
- The submission considers treatment with golimumab at two points in the clinical pathway: after the failure of conventional DMARDs, and after the failure of conventional DMARDs and a first tumour necrosis factor (TNF)-α inhibitor. Is treatment with golimumab at these points in the clinical pathway considered appropriate?
- Patients taking part in the golimumab randomised controlled trials had active disease, defined as persistent disease activity with at least four swollen and four tender joints (or at least six swollen and six tender joints for Kay et al 2008). A high proportion of these patients were also receiving glucocorticoid therapy. Are the populations in the clinical trials generalisable to those in UK clinical practice?
- The manufacturer reports that only limited data are available for radiographic progression. In addition, SF-36 data were not provided. Are the outcomes in the manufacturer's submission considered appropriate?
- Golimumab is a type of TNF-α inhibitor. There are currently four other TNF-α inhibitors (adalimumab, etanercept, infliximab and certolizumab pegol) that NICE recommends as treatment options:
  - Has golimumab shown efficacy in comparison with placebo, and with the other comparators included in the scope for the appraisal (conventional DMARDs and other biological treatments)?
  - Should the TNF-α inhibitors be considered as a group with similar clinical effectiveness?

  - Is it appropriate to assume that golimumab has a comparable safety profile to the other TNF-α inhibitors?
  - Should the absence of long-term data be considered?

Cost effectiveness

- For a subgroup of patients (that is, those weighing over 100 kg) whose disease has not responded to 50 mg of golimumab, the dose may be increased to 100 mg. However, the manufacturer's economic model only includes the 50 mg dose of golimumab. What is the Committee's view on excluding the 100 mg dose from the model?
- The economic model only includes ACR20 and ACR50 response rates.
  - What is the Committee's view on omitting the ACR70 data from the model?
  - Is ACR20 response rate appropriate as a criterion for continuing treatment at 6 months?
- The economic model assumes that golimumab delays the underlying progression of disease while on treatment (that is, Health Assessment Questionnaire [HAQ] progression) to the same degree as the other TNF-α inhibitors, but to a greater degree than rituximab and conventional DMARDs:
  - What is the Committee's view on the HAQ progression rate estimates?
  - Does the submission provide evidence that supports using different HAQ progression rate estimates for golimumab and rituximab?
- The economic model assumes that the initial effect of treatment is maintained until treatment stops. When treatment is stopped the worsening of disease is to the same degree as the initial gain from starting treatment. Does the Committee consider that the assumptions about maintenance of effect and loss of initial effect when treatment is stopped are appropriate?
- The manufacturer's model assumes that rituximab is provided every 6 months. NICE guidance states that rituximab should not be provided

more frequently than every 6 months. What is the most appropriate assumption about when to re-administer rituximab?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with moderate to severe active rheumatoid arthritis whose disease has had an inadequate response to DMARDs including methotrexate
Intervention	Golimumab in combination with methotrexate
Comparators	Management strategies involving DMARDs without golimumab, including treatment with: • conventional DMARDs (for example, sulfasalazine, leflunomide) • biological drugs (including adalimumab, etanercept, infliximab, rituximab, certolizumab pegol).
Outcomes	The outcome measures addressed include: • disease activity • physical function • joint damage • pain • mortality • fatigue • radiological progression • adverse effects of treatment • health-related quality of life Extra-articular manifestations of disease were not included because they are not routinely reported in randomised controlled trials.
Economic evaluation	• Cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year (QALY). • The time horizon considered is the lifetime of the patient. • Costs are considered from an NHS and Personal Social Services perspective.

1.2 Evidence Review Group comments

1.2.1 Population

In the decision problem the manufacturer specifies the population as adults with moderate to severe active rheumatoid arthritis whose disease has had an

inadequate response to DMARDs including methotrexate, which is consistent with the licensed indication. The ERG noted that this is slightly different from the final scope issued by NICE, which did not specifically mention methotrexate. The manufacturer's submission considers patients who have never received a TNF-α inhibitor (DMARD experienced population) separately from patients who have had previous therapy with a TNF-α inhibitor (TNF-α inhibitor experienced population). The ERG considered this to be a reasonable approach because the treatment options available to patients with rheumatoid arthritis under current NICE guidance differ depending on whether they have had previous therapy with a TNF-α inhibitor. The final scope also specified that, if evidence allowed, the appraisal would consider subgroups of people defined by the baseline severity of their rheumatoid arthritis. Analyses based on moderate and severe baseline disease activity were submitted by the manufacturer after completion of the ERG report.

1.2.2 Intervention

The intervention described in the decision problem is golimumab in combination with methotrexate. The current licensed dosage of golimumab is 50 mg administered once a month. The licence indicates that for patients weighing more than 100 kg who do not achieve an adequate clinical response after three or four doses an increase in the dosage to 100 mg once a month may be considered. The ERG reported that the dosing regimen considered in the model does not take into account the likelihood of dose increases from 50 to 100 mg.

1.2.3 Comparators

The ERG commented that the comparators listed in the decision problem excluded tocilizumab and abatacept, which are listed in the final scope. After a request for clarification the manufacturer explained that, at the time it made its submission, NICE had not published final guidance on these drugs. Therefore, the manufacturer excluded abatacept and tocilizumab as comparators from the TNF-α inhibitor experienced meta-analyses. The ERG suggested that it

would be useful to compare golimumab with other TNF-α inhibitors or tocilizumab when these treatments are used after the failure of a first TNF-α inhibitor because NICE recommends these treatment options when rituximab therapy is contraindicated or stopped because of an adverse event. The ERG also suggested that it would be useful to compare golimumab with tocilizumab when it is used after a patient's disease fails to respond to at least one TNF-α inhibitor and rituximab, although it recognised that there are no trials with golimumab in this population.

1.2.4 Outcomes

The ERG noted that data on mortality, fatigue, radiological progression, extra-articular disease manifestations and SF-36 were not included in the submission. After a request for clarification, the manufacturer provided data on mortality and radiological progression. Data on joint damage and pain were included in the table of baseline characteristics but the ERG noted that this would not address the impact of treatment on these outcomes. The ERG also commented that ACR70 is not included as an outcome in the economic model.

1.2.5 Economic evaluation

The ERG commented that the incremental analysis was conducted separately for the DMARD experienced and the TNF-α inhibitor experienced populations. Therefore, it would not be possible to evaluate whether it is more cost-effective to use golimumab after the failure of DMARDs or after the failure of a TNF-α inhibitor.

1.3 Statements from professional/patient groups and nominated experts

The experts agreed that treatment with golimumab has an advantage over other TNF-α inhibitors because it is administered subcutaneously, which is often preferred by patients, and only provided once every 4 weeks, which is less frequent than for other TNF-α inhibitors provided by subcutaneous

injection. However, they commented that no head-to-head trials have been carried out showing that golimumab produces better outcomes than other TNF-α inhibitors. They felt that the side-effect profile was unlikely to differ from those of other established TNF-α inhibitors. They considered that side effects such as an increased risk of infection, and others which are usually associated with biological drugs, are expected to apply to golimumab. The experts noted that the licensed indication for golimumab includes self-administration by patients. They suggested that, if it is suitable, the training procedures currently in place for etanercept self-injection should be relevant for golimumab. They expected that golimumab would be used in secondary care, and would be covered by existing resources.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The submission considered patients who had never received a TNF-α inhibitor (DMARD experienced population) separately from patients who had had previous therapy with a TNF-α inhibitor (TNF-α inhibitor experienced population). It included a phase III randomised controlled trial (GO-FORWARD) and a phase II dose-ranging trial (Kay et al. 2008) for the DMARD experienced population. There were four and five groups respectively in the two trials. However, the manufacturer's submission focused on the groups that had received the licensed dose of 50 mg golimumab every 4 weeks.

GO-FORWARD

GO-FORWARD is a multicentre randomised double-blind trial that compared 50 mg golimumab (every 4 weeks) plus methotrexate (≥15 mg every week) with placebo plus methotrexate. Patients taking part in the trial had had active rheumatoid arthritis (defined as persistent disease activity with at least four swollen joints and four tender joints) for at least 3 months and had received

methotrexate for at least 3 months. The trial included a controlled phase to 24 weeks and an open-label extension to 5 years. An 'early escape' for people whose disease did not respond to treatment was incorporated into the trial at 16 weeks. The primary outcome measures were the proportion of patients achieving an ACR20 response at 14 weeks and an improvement from baseline in the HAQ disability index (HAQ-DI) score at 24 weeks. Of the 440 patients taking part in GO-FORWARD, 133 were randomised to placebo plus methotrexate and 89 were randomised to 50 mg golimumab plus methotrexate. The patient flow diagram of GO-FORWARD can be found on page 104 of the manufacturer's submission. The baseline characteristics of the patients are summarised in table 116 of the manufacturer's submission.

The results of GO-FORWARD are summarised in table 1. A significantly greater proportion of patients on 50 mg golimumab plus methotrexate achieved an ACR20 response at 14 weeks compared with placebo plus methotrexate. Improvement in HAQ-DI at 24 weeks was [redacted] in the 50 mg golimumab plus methotrexate group compared with the placebo plus methotrexate group.

Table 1 Summary of key GO-FORWARD efficacy data

Outcome	Golimumab 50 mg plus methotrexate	Placebo plus methotrexate	Relative risk (95% confidence interval)	p-value
Primary outcomes				
ACR20 response at 14 weeks	49/89 (55.1%)	44/133 (33.1%)	NR	p = 0.001
Improvement in HAQ-DI score at 24 weeks	Mean [redacted] SD [redacted]	Mean [redacted] SD [redacted]	NR	[redacted]
Secondary outcomes				
ACR20 response at 24 weeks	53/89 (59.6%)	37/133 (27.8%)	2.14 (1.55, 2.96)	p < 0.001
ACR50 response at 24 weeks	33/89 (37.1%)	18/133 (13.5%)	2.74 (1.65, 4.55)	p < 0.001
ACR70 response at 24 weeks	18/89 (20.2%)	7/133 (5.3%)	3.84 (1.67, 8.82)	p < 0.001
ACR: American College of Rheumatology; NR: not reported				

Kay et al. (2008)

Kay et al. (2008) is a multicentre randomised double-blind study that compared 50 mg golimumab (every 4 weeks) plus methotrexate (≥10 mg every week) with placebo plus methotrexate. Patients taking part in the study had had active rheumatoid arthritis (defined as persistent disease activity with at least six swollen joints and six tender joints) for at least 3 months and had been treated with methotrexate for at least 3 months. The primary outcome was the proportion of patients achieving an ACR20 response at 16 weeks. Of the 172 patients taking part in the study, 35 were randomised to the placebo plus methotrexate group and 35 to the 50 mg golimumab plus methotrexate group. Summary information about patients' baseline characteristics are presented on page 39 of the Response to NICE clarification letter.

The primary outcome data were not presented for the 50 mg golimumab group. However, combined data for all the golimumab groups (including the

unlicensed doses) showed that the golimumab plus methotraxate groups had a statistically significantly higher proportion of subjects achieving an ACR20 response at 16 weeks than the placebo plus methotrexate group (p = 0.010) (see page 40 of the Response to NICE clarification letter). Data at 24 weeks showed that a greater proportion of patients receiving 50 mg golimumab plus methotrexate achieved an ACR20, ACR50 and ACR70 response compared with those receiving placebo plus methotrexate (table 2).

Table 2 Summary of ACR20, ACR50 and ACR70 response data at 24 weeks from Kay et al.

Outcome	Golimumab 50 mg plus methotrexate	Placebo plus methotrexate	Relative risk (95% confidence interval)
ACR20 response at 24 weeks	26/35 (74.3%)	16/35 (45.7%)	1.63 (1.08, 2.45)
ACR50 response at 24 weeks	14/35 (40%)	4/35 (11.4%)	3.50 (1.28, 9.59)
ACR70 response at 24 weeks	7/35 (20%)	2/35 (5.7%)	3.50 (0.78, 15.69)
ACR: American College of Rheumatology			

GO-AFTER

The manufacturer included a single phase III randomised controlled trial (GO-AFTER) for the TNF-α inhibitor experienced population. The trial had three groups but the manufacturer's submission only focused on the placebo group and the group receiving 50 mg golimumab. It was a randomised double-blind placebo-controlled trial and the patients taking part had had active rheumatoid arthritis (defined as persistent disease activity with at least four swollen joints and four tender joints) for at least 3 months and had been treated with at least one dose of a TNF-α inhibitor (etanercept, adalimumab or infliximab). The primary outcome was the proportion of patients achieving an ACR20 response at 14 weeks. The duration of follow up was 24 weeks. However, an 'early escape' for people whose disease did not respond to treatment was incorporated into the trial at 16 weeks. Of the 461 patients, 155 were randomised to the placebo group and 153 to the 50 mg golimumab group. The

patient flow diagram can be found on page 110of the manufacturer's submission. The baseline characteristics of the patients are summarised in table 121 of the manufacturer's submission.

The key efficacy data are presented in table 3 and show that a significantly higher proportion of patients on 50 mg golimumab achieved an ACR20 response at 14 weeks compared with placebo.

Table 3 Summary of key GO-AFTER response data

Outcome	Golimumab 50 mg	Placebo	Relative risk (95% confidence interval)	p-value
Primary outcome				
ACR20 response at 14 weeks	54/153 (35.3%)	28/155 (18.1%)	NR	p<0.001
Secondary outcomes				
Improvement in HAQ-DI score at 24 weeks	Mean [redacted] SD [redacted]	Mean [redacted] SD [redacted]	NR	[redacted]
ACR20 response at 24 weeks	52/153 (34.0%)	26/155 (16.8%)	2.03 (1.34, 3.07)	p<0.001
ACR50 response at 24 weeks	28/153 (18.3%)	8/155 (5.2%)	3.55 (1.67, 7.53)	p<0.001
ACR70 response at 24 weeks	18/153 (11.8%)	5/155 (3.2%)	3.65 (1.39, 9.58)	p=0.004
ACR: American College of Rheumatology; NR: not reported				

Mixed treatment comparison and indirect comparison

No head-to-head trials were available analysing the efficacy of golimumab versus the comparators in the appraisal. Therefore, the manufacturer searched for trials of comparator interventions. The manufacturer presents the results of separate meta-analyses of the trial data for golimumab and each of the comparators (page 65 of the manufacturer's submission). In addition, mixed treatment comparison and indirect comparison analyses were undertaken to estimate the relative effect of golimumab versus the comparators (adalimumab, certolizumab pegol, etanercept, infliximab and

rituximab). This pre-meeting briefing summarises the mixed treatment comparison and indirect comparison analyses.

DMARD experienced population

Twenty trials were included in the mixed treatment comparison for the DMARD experienced population

- two trials comparing golimumab with placebo (GO-FORWARD; Kay et al. 2008)
- seven trials comparing adalimumab with placebo
- two trials comparing certolizumab pegol with placebo
- four trials comparing etanercept with placebo
- five trials comparing infliximab with placebo.

The results from the random effects model are presented in table 4. For ACR20, ACR50 and ACR70 response rates, there were no statistically significant differences when golimumab was compared with adalimumab, certolizumab pegol, etanercept or infliximab. For each ACR response, golimumab was superior to placebo, with a statistically significant difference demonstrated. The results from the fixed effects models are presented on page 68 of the ERG report.

Table 4 Results of the mixed treatment comparison for the DMARD experienced population (taken from tables 13–15 of the ERG report)

	Random effects model					
	ACR20		ACR50		ACR70	
	Relative risk (median)	95% credible interval	Relative risk (median)	95% credible interval	Relative risk (median)	95% credible interval
Golimumab vs placebo	2.17	1.27, 3.00	3.22	1.54, 5.74	4.20	1.79, 9.68
Golimumab vs adalimumab	0.98	0.55, 1.46	0.90	0.40, 1.76	0.75	0.28, 1.86
Golimumab vs certolizumab pegol	0.72	0.41, 1.06	0.63	0.27, 1.31	0.47	0.16, 1.35
Golimumab vs etanercept	0.93	0.51, 1.43	0.98	0.40, 1.99	0.32	0.09, 1.15
Golimumab vs infliximab	1.05	0.57, 1.65	0.99	0.42, 2.04	1.16	0.40, 3.00
ACR: American College of Rheumatology						

Sensitivity analyses were performed for ACR20 and ACR50 responses in which the TEMPO etanercept trial was excluded because of a greater response within the placebo arm compared with other studies. The findings indicated that the exclusion of the TEMPO trial resulted in raised relative risks for ACR20 and ACR50, indicating increased efficacy for etanercept in comparison with golimumab. However, these results were only statistically significant in the fixed effects model for the ACR20 response. The exclusion of the TEMPO trial also altered the relative estimates for golimumab in comparison with the other treatments. For the comparison of golimumab and certolizumab pegol, these differences were statistically significant in the fixed effects model and for ACR20 in the random effects model favouring certolizumab pegol (see page 84 of the manufacturer's submission).

TNF-α inhibitor experienced population

Two trials were used in the indirect comparison analyses of golimumab (GO-AFTER) and rituximab (REFLEX) for the TNF-α inhibitor experienced

population. In these analyses (based on the methods developed by Bucher et al. 1997), the efficacies of golimumab and rituximab were indirectly compared with placebo as the comparator. Although the mean values favoured rituximab, there were no statistically significant differences between golimumab and rituximab for any of the outcome measures (table 5).

Table 5 Results of an indirect comparison in the TNF-α inhibitor experienced population (taken from table 16 of the ERG report)

	Golimumab vs rituximab	
Outcome	**Relative risk Mean indirect estimate**	**95% confidence interval**
ACR20 at 6 months	0.71	0.42, 1.20
ACR50 at 6 months	0.66	0.25, 1.76
ACR70 at 6 months	0.30	0.05, 1.66
ACR: American College of Rheumatology		

Safety

DMARD experienced population

In the GO-FORWARD study there appeared to be a slightly higher incidence of adverse events including hypertension, serious adverse events, infections, serious infections, and injection-site disorders in the golimumab 50 mg arm at 16 and 24 weeks (table 119 on page 107 of the manufacturer's submission). In Kay et al. (2008) the numbers of patients experiencing at least one adverse event and serious adverse events were higher in the 50 mg golimumab plus methotrexate group than in the placebo plus methotrexate group.

A mixed treatment comparison was carried out for selected safety outcomes. Golimumab was estimated to have more serious adverse events than all comparators except certolizumab pegol, although there was considerable uncertainty as shown by the wide credible intervals. The estimated rate of serious infections for golimumab was similar to the rates for infliximab and etanercept, which were the lowest for the interventions, although all had wide confidence intervals. Golimumab was estimated to have the fewest injection

site reactions and discontinuations because of adverse events, although the values for all interventions were subject to considerable uncertainty. A summary of the results from the random effects model is presented in table 6. The results of the fixed effect model are given on pages 93 and 94 of the ERG report.

Table 6 Summary of the mixed treatment comparison for adverse events in the DMARD experienced population (taken from tables 36, 37 and 39 of the ERG report)

	Random effects model					
	Serious adverse events		Serious infections		Discontinuation because of adverse events	
	Relative risk (median)	95% credible interval	Relative risk (median)	95% credible interval	Relative risk (median)	95% credible interval
Golimumab vs placebo	1.33	0.51, 3.39	1.13	0.13, 10.46	0.59	0.14, 2.02
Golimumab vs adalimumab	1.25	0.44, 3.48	0.40	0.03, 4.8	0.33	0.07, 1.26
Golimumab vs certolizumab pegol	0.63	0.2, 1.92	0.02	0, 0.93	0.20	0.04, 0.95
Golimumab vs etanercept	1.46	0.46, 4.52	1.10	0.07, 17.77	0.68	0.14, 2.67
Golimumab vs infliximab	1.39	0.49, 3.96	0.99	0.09, 11.71	0.29	0.06, 1.17

TNF-α inhibitor experienced population

No major differences in reported adverse events were evident in the GO-AFTER study at 24 weeks (page151 of the ERG report). The number of serious adverse events at 24 weeks was slightly lower in the 50 mg golimumab plus methotrexate group compared with the placebo plus methotrexate group. In terms of serious infections, 5% of the 50 mg golimumab plus methotrexate group experienced serious infections (no data presented for the placebo group).

The indirect comparison suggested that the relative risks for serious adverse events were similar for golimumab and rituximab, although there was considerable uncertainty. The relative risk estimate for serious infections was slightly lower for golimumab compared with rituximab, however this was associated with wide confidence intervals. Golimumab was associated with lower rates of discontinuation due to adverse events with a statistically significant difference. A summary of the results from the fixed effects model is presented in table 7.

Table 7 Summary of the mixed treatment comparison for adverse events in the TNF-α inhibitor experienced population (taken from tables 40–42 of the ERG report)

	Fixed effects model					
	Serious adverse events		Serious infections		Discontinuation because of adverse events	
	Relative risk (median)	95% credible interval	Relative risk (median)	95% credible interval	Relative risk (median)	95% credible interval
Golimumab vs placebo	0.74	0.34,1.53	1.02	0.28, 3.62	0.43	0.11, 1.33
Golimumab vs rituximab	1.00	0.38, 2.55	0.61	0.09, 3.75	0.15	0.02, 0.91

Mortality

No differences in mortality between golimumab and the comparators were apparent (see table 1 in the Response to NICE clarification letter).

2.2 Evidence Review Group comments

Overall, the ERG considered the clinical-effectiveness review methods and results to be reasonably clearly presented, with adequate systematic searches conducted. All the relevant randomised controlled trials for golimumab and comparators appeared to have been included and the golimumab trials were of reasonable methodological quality. The ERG considered that the mixed treatment comparisons and indirect comparisons used appropriate trials to inform the networks of evidence.

The ERG commented that the populations in GO-FORWARD and Kay et al. (2008) were generally representative of the UK population, although the proportion of patients receiving glucocorticoid therapy was higher in the GO-FORWARD trial than the UK average. Similarly, for the GO-AFTER population, it was noted that steroid use in this study may potentially be higher than in the UK population.

The ERG noted that the evidence did not include some of the comparators listed in the final scope, and that health-related quality of life and fatigue were not adequately addressed in the clinical evidence section of the submission.

The ERG noted inconsistencies between the data presented for ACR20 and ACR50 responses in Kay et al. (2008). Different values were presented in the original study publication (week 16) and in the efficacy meta-analyses in the manufacturer's submission. The ERG is unclear how the original efficacy data from Kay et al. (2008) have been derived and handled in the meta-analyses.

The ERG commented on the complexities involved in comparing data across the interventions because response rates may be influenced by changes in patient populations over time. They noted that the certolizumab pegol trials had a higher ratio of ACR responses on active treatment compared with placebo which meant that these trials may not be comparable with the trials of other TNF-α inhibitors. The ERG suggested that one factor contributing to the results observed in the certolizumab pegol trials may be that patients stopped receiving treatment at 12 weeks if there was no response, which meant that slower responses in the placebo group were not detected. The ERG noted the manufacturer's sensitivity analyses excluding the TEMPO trial and considered these appropriate analyses to complete.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer submitted two decision-analytic Markov models developed in Microsoft Excel. The models evaluated golimumab as part of a sequence of treatments (page 125 of the manufacturer's submission) in two different patient populations:

- DMARD experienced population – comparing golimumab with TNF-α inhibitors (etanercept, adalimumab, infliximab and certolizumab pegol) and methotrexate in patients whose disease had had an inadequate response to two DMARDs
- TNF-α inhibitor experienced population – comparing golimumab with rituximab and methotrexate in patients whose disease had had an inadequate response on two DMARDs and a TNF-α inhibitor.

At the start of the models patients were aged 50 years in the DMARD experienced population and 54 years in the TNF-α inhibitor experienced population. The time horizon of the models was 45 years, reflecting a lifetime perspective.

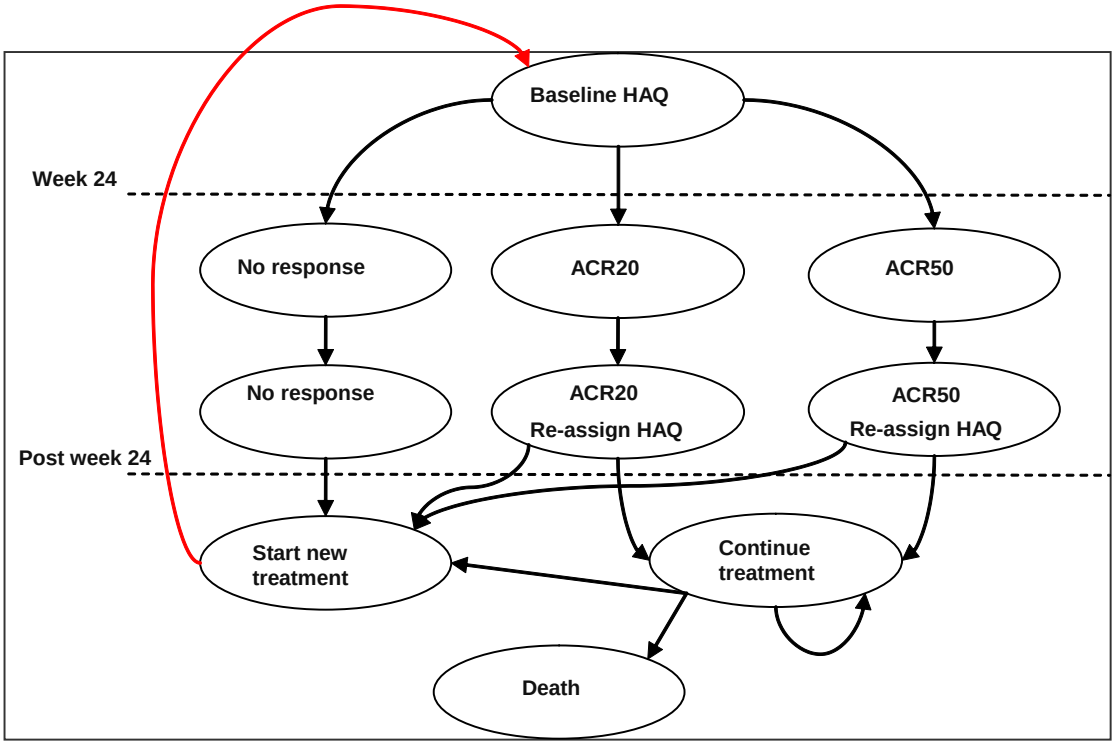
All treatments were given with methotrexate. Methotrexate monotherapy was included as a comparator in each model because it represented the placebo arm in the indirect comparison and mixed treatment analysis. Technologies being appraised by NICE at the time of the manufacturer's submission (tocilizumab, abatacept and the use of etanercept, infliximab and adalimumab after the failure of a first TNF-α inhibitor) were not included as comparators.

Model structure

Both models estimated a patient's disease level based on their HAQ-DI score. Baseline HAQ was derived from the baseline characteristics of the

GO-FORWARD and GO-AFTER trials: 1.41 and 1.58 respectively. The model reassigned a HAQ score every cycle.

Figure 1 Model (from page 123of the manufacturer's submission)



Patients progressed to the next treatment if they did not achieve at least an ACR20 response at 6 months, or if they stopped treatment because of either a lack of efficacy or an adverse event. In both models, patients progressed to leflunomide, gold, azathioprine, ciclosporin and then palliative care. While patients were within a health state, it was assumed that their disease severity increased over time. This was modelled with an annual worsening of HAQ score (that is, a HAQ progression rate). DMARDs, TNF-α inhibitors, rituximab and palliative care all had differential HAQ progression rates. The annual worsening of the HAQ score for a patient being treated with DMARDs was 0.045, for TNF-α inhibitors it was 0.00, for rituximab it was 0.045 and for palliative care it was 0.09.

The models contained three health states: ACR20 response, ACR50 response and no response. The probability of being in a health state for golimumab and methorexate monotherapy was derived from the GO-FORWARD and GO-AFTER trials. For golimumab, the probability of an ACR20 response was 0.213 and 0.157 respectively, and of an ACR50 response was 0.382 and 0.183 respectively. For the other comparators the response for golimumab was adjusted from the relative effects derived from the mixed trial comparison and an indirect comparison of the clinical trial data (see page 134 of the manufacturer's submission).

For each ACR response criteria the corresponding change in HAQ-DI was calculated based on data from the GO-FORWARD and GO-AFTER clinical trials. The HAQ-DI was in turn mapped to EQ-5D using an equation used in previous NICE guidance (TA130 Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis). Examples of the resulting utility estimates are summarised in table 8.

Table 8 Utility scores at 24 weeks (from page 141 of the manufacturer's submission)

Health state	Methotrexate experienced (GO-FORWARD)	TNF-α inhibitor experienced (GO-AFTER)
Baseline	0.401	0.343
No response	0.461	0.376
ACR 20	0.581	0.466
ACR 50	0.638	0.572

Costs relating to treatment, administration, monitoring and hospitalisation (2008 Reference Costs and 2009 Unit Costs) were included in the economic models (see page 148 of the manufacturer's submission). Drug and administration costs in the first 6 months and after the first 6 months are summarised in table 9 (see also page 152 of the manufacturer's submission). It was assumed that a course of rituximab was given once every 6 months.

Joint replacement was not included in the model. Costs and QALYs were discounted at a rate of 3.5%.

Table 9 Acquisition and administration costs associated with the technology in the economic model

	Cost per dose (£)	No. doses in first 6 months	No. doses after 6 months	Cost per administration[4] (£)	Total cost in first 6 months (£)	Total cost after 6 months (£)
Golimumab	774.58	6	6	34.00	4681.48	4647.48
Adalimumab	357.50	13	13	34.00	4681.50	4647.50
Infliximab[1]	419.62	13.35	8.6775	55.00	6336.18	4118.52
Etanercept	89.38	52	52	34.00	4681.76	4647.76
Rituximab[2]	873.50	6	4	76.00	5694.90	3796.60
Certolizumab pegol[3]	357.50	6	13	34.00	2179.00	4647.50

[1] Each infusion of infliximab is assumed to require 2.67 doses. In the first 6 months 13.35 doses equates to 5 infusions and in subsequent 6 months 3.25 infusions

[2]A course of rituximab requires 4 doses. In the first 6 months 6 doses equates to 1.5 infusions and in subsequent 6 months to 1 infusion.

[3]The cost and doses in the first 6 months are adjusted for a patient access scheme that provides the drug cost for the first 12 weeks at no cost.

[4]Subcutaneous treatments (golimumab, adalimumab, etanercept and certolizumab pegol) have a single administration cost at the start of treatment of £34. Treatments provided by intravenous infusion (infliximab and rituximab) have an infusion cost for each infusion. This is estimated to be £34 with an additional £4.81 for each subsequent hour spent in hospital.

The impact of parameter uncertainty was estimated in a probabilistic sensitivity analysis (PSA). Scenario analyses were run on key parameters.

An incremental analysis was performed within each population. However an incremental analysis was not possible between the populations, and so the optimal position of golimumab cannot be determined.

Results

DMARD experienced population

The deterministic results for the DMARD experienced population are presented in table 10 (reproduced from table 49 of the ERG report, page 121).

Table 10 DMARD experienced population – manufacturer's base-case results of the economic analysis

Technology	Total costs (£)	Total QALYs	Incremental analysis – comparison made to next least effective non-dominated strategy ICER (per QALY gained) (£)	ICER (per QALY gained) vs methotrexate[a] (£)
Methotrexate	35,869	4.569	–	–
Infliximab	69,899	5.651	Dominated by golimumab	31,451
Certolizumab pegol	73,571	5.768	Dominated by golimumab	31,444
Adalimumab	66,875	5.792	Extendedly dominated by etanercept	25,352
Golimumab	67,747	5.827	Extendedly dominated by etanercept	25,340
Etanercept	74,208	6.133	24,513	24,513

[a] Indicates cost-effectiveness when all other biological drugs are contraindicated.

Infliximab and certolizumab pegol are both dominated by golimumab because golimumab is more effective and less costly. However, the incremental analysis shows that adalimumab and golimumab are both extendedly dominated by etanercept. Etanercept generates the most QALYs of any strategy, but at a lower cost per QALY ratio.

Base-case PSA results for the DMARD experienced population

For the DMARD experienced population, the cost-effectiveness results based on the mean costs and QALYs from the PSA are consistent with the deterministic analysis. At a willingness to pay threshold of £20,000 per QALY gained, golimumab is the most cost-effective intervention in 5% of PSA samples, methotrexate is most cost-effective in 56%, followed by etanercept in 17%. At a willingness to pay threshold of £30,000 per QALY gained, golimumab is the most cost-effective intervention in 8% of samples, etanercept is most cost-effective in 32%, followed by methotrexate in 24%.

TNF-α inhibitor experienced population

The results for the deterministic base-case analysis of golimumab in a TNF-α inhibitor experienced population are summarised in table 11 (reproduced from table 50 of the ERG report, page 123).

Table 11 TNF-α inhibitor experienced population – manufacturer's base-case results of the economic analysis

Technology	Total costs (£)	Total QALYs	Incremental analysis – comparison made to next least effective non-dominated strategy ICER (per QALY gained) (£)	ICER (per QALY gained) vs methotrexate[a] (£)
Methotrexate	33,673	3.129	–	–
Rituximab	50,206	3.523	Dominated by golimumab	41,961
Golimumab	50,175	3.712	28,305	28,305

[a] Indicates cost-effectiveness when all other biological drugs are contraindicated.

Table 11 shows that rituximab is dominated by golimumab because golimumab is less costly and more effective. Golimumab compared with methotrexate has an ICER of £28,305.

Base-case PSA results for the TNF-α inhibitor experienced population

In the TNF-α inhibitor experienced population, rituximab is extendedly dominated by golimumab based on the mean costs and QALYs from the PSA. Golimumab has an ICER of £29,100 compared with methotrexate. At a willingness to pay threshold of £20,000 per QALY gained, golimumab is most cost-effective in 5% of PSA samples and methotrexate is most cost-effective in 90%. At a willingness to pay threshold of £30,000 per QALY gained, golimumab and methotrexate have a similar probability of being most cost-effective (46% and 44% respectively).

Sensitivity analysis

The manufacturer undertook a scenario analysis to examine what happens when a patient withdraws from treatment. The base-case analysis assumes that on stopping treatment the loss of effect is equal to the gain achieved. This

assumes that there is a long term benefit accrued by delaying disease progression from receiving treatment. The manufacturer undertook a sensitivity analysis with the HAQ rebound causing the HAQ to return to the population natural history level. This assumption suggests that there are no long-term benefits of active interventions. In the DMARD experienced population, the incremental analysis shows that infliximab and etanercept are dominated strategies, and golimumab and adalimumab are extendedly dominated by certolizumab pegol. The ICERs for all the treatments compared with methotrexate increase to above 30,000 per QALY gained. In the TNF-α inhibitor experienced population rituximab is dominated by golimumab but the ICER for golimumab compared with methotrexate rises to over £42,000 per QALY gained (see page 128 of the ERG report).

3.2 Evidence Review Group comments

The ERG noted that the model results (total costs and QALYs, time in states, HAQ scores and incremental costs and QALYS) appeared plausible given the parameter inputs. It commented that the model was generally of a high quality. The ERG identified some programming errors in the model that it corrected. However, these errors did not change the conclusion that, compared with methotrexate, golimumab has an ICER that is comparable to other TNF-α inhibitors but golimumab is never the optimal TNF inhibitor strategy.

The ERG commented that they considered that it would have been appropriate to include the ACR70 response data in the model so that all the available clinical evidence is used to evaluate golimumab. The manufacturer justified the exclusion of these data by stating that there was not a statistically significant difference between golimumab and the comparators and that incorporating this outcome would only add an element of uncertainty to the model inputs. The ERG felt that this reason was not justified because there was not a statistically significant difference in the ACR20 and ACR50 response data for golimumab and the comparators. However, the ERG noted

that adding this outcome to the model would have meant almost completely rebuilding the model and this was not possible in the exploratory analyses.

The ERG felt that for the TNF-α inhibitor experienced population there was considerable uncertainty in the HAQ progression rate estimates and the re-administration frequency of rituximab. The ERG commented that the manufacturer assumed a HAQ progression rate equal to the rate for DMARDs rather than for TNF-α inhibitors, which may underestimate the benefit of rituximab. The ERG commented that the model assumes that rituximab is re-administered every 6 months but it felt that 9 months would be more reflective of current clinical practice. The ERG undertook a number of exploratory analyses, which are discussed below.

Results of the ERG exploratory analyses

The ERG undertook a step-wise exploratory analysis for a number of alternative assumptions.

DMARD experienced model

1. Updated unit and reference costs

The original model used 2006 Reference Case costs and 2008 Unit Costs. However, after clarification, the manufacturer incorporated 2008 Reference Costs and 2009 Unit Costs. Updating the unit and reference costs had little impact on the incremental costs for the different treatments, and so the resulting ICERs did not change substantially (see page 135 of the ERG report). These revised unit costs are included in analysis 2.

2. Infliximab costs and HAQ decrements in certolizumab pegol arm corrected

The ERG identified an error in the Markov model sheets for infliximab in the DMARD experienced population, which resulted in a cost being allocated when a patient dies. There was also an error in the modelling of HAQ decrements for certolizumab pegol. The method used is different from that used for comparator drugs, however there is no difference in the methods reported in the submission. Because each of these errors only affect a single

comparator, both were corrected. Correcting the infliximab costs reduces the total cost of infliximab treatment, and it is no longer dominated by adalimumab. Correcting the HAQ progression in the certolizumab pegol arm means that it is the most cost-effective intervention instead of etanercept (see page 135 of the ERG report). These changes are included in analysis 3.

3. Using the mixed treatment comparison to estimate the relative risk of placebo compared with golimumab

The economic model used the event rates from the GO-FOWARD trial to estimate the probability of ACR response and the probability of stopping treatment because of adverse event at 6 months in the golimumab and placebo arms. However, the model used the mixed treatment comparison to estimate the rates of these events for the comparators; this approach excludes the evidence from Kay et al. (2008). In the exploratory analysis the ERG used the mixed treatment comparison, incorporating the evidence from Kay et al. (2008), to estimate the probability of these outcomes in the placebo group, which is used to populate the methotrexate arm of the economic model. Using the mixed treatment comparison rather than the GO-FORWARD study alone to inform the golimumab versus methotrexate comparison did not substantially alter the results.

Table12 Cumulative impact of changes on the cost-effectiveness results for the DMARD experienced population (table 57 in the ERG report)

Technology	Total costs (£)	Total QALYs	Incremental analysis – comparison made to next least effective non-dominated strategy ICER (per QALY gained) (£)	ICER (per QALY gained) vs methotrexate[a] (£)
Methotrexate	39,611	4.550	–	–
Infliximab	66,144	5.649	Extendedly dominated by certolizumab pegol	24,137
Adalimumab	70,376	5.790	Extendedly dominated by certolizumab pegol	24,800
Golimumab	71,229	5.825	Extendedly dominated by certolizumab pegol	24,794
Etanercept	77,548	6.131	Dominated by certolizumab pegol	23,990
Certolizumab pegol	76,868	6.341	20,800	20,800

[a] Indicates cost-effectiveness when all other biological drugs are contraindicated.

TNF-α inhibitor experienced model

4. Updated unit and reference costs

The costs were updated for the TNF-α inhibitor experienced population, as described for the DMARD experienced population in analysis 1. These changes were included in analysis 5 (see page 136 of the ERG report).

5. Rituximab – zero HAQ progression rate

The base-case model assumes that a person receiving rituximab has an annual HAQ progression rate equal to conventional DMARDs (0.045) as opposed to TNF-α inhibitors (zero). The ERG considered that this assumption underestimates the benefit of rituximab, and so amended the model to assume that rituximab has a zero HAQ progression rate (equal to that of TNF-α inhibitors). This change is included analysis 6. Separate scenario analyses were also completed using: an intermediate rate of 0.03 for rituximab and 0.00 for TNF-α inhibitors; and 0.03 for all biological drugs (see page 137 of the ERG report).

6. Rituximab retreatment every 9 months

The ERG considered that assuming retreatment with rituximab every 9 months on average would be more reflective of current clinical practice. This assumption was incorporated in the model, with every patient receiving two infusions in the first 6 months, and then an average of one infusion every 9 months.

Table13 Cumulative impact of changes on the cost-effectiveness results for the TNF-α inhibitor experienced population (table 62 of the ERG report)

Technology	Total costs (£)	Total QALYs	Incremental analysis – comparison made to next least effective non-dominated strategy ICER (per QALY gained) (£)	ICER (per QALY gained) vs methotrexate[a] (£)
Methotrexate	37,134	3.129	–	–
Golimumab	53,519	3.711	Dominated by rituximab	28,115
Rituximab	44,897	3.898	10,088	10,088

[a] Indicates cost-effectiveness when all other biological drugs contraindicated.

The analyses show that the model is sensitive to the assumptions made about rituximab and TNF-α inhibitor HAQ progression. If rituximab is assumed to be re-administered every 9 months, then it dominates golimumab.

The PSA for the ERG's preferred scenario is comparable to that of the deterministic results. The probabilistic analysis for this scenario estimates that rituximab dominates golimumab, and rituximab is the most cost-effective strategy in over 85% of PSA samples when considering an ICER threshold between £20,000 and £30,000 per QALY gained.

Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), University of Sheffield:

- Jackson R, et al. Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs: a single technology appraisal, September 2010

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Schering Plough (part of MSD)

II Professional/specialist, patient/carer and other groups:

- British Health Professionals in Rheumatology
- British Society for Rheumatology
- National Rheumatoid Arthritis Society
- NHS Dorset (Torbay PCT)
- NHS North of Tyne (working on behalf of Newcastle and North Tyneside Primary Care Trusts and Northumberland Care Trust)
- NICE RA Management Guideline Development Group
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal Collage of Pathologists

C Additional references used: None

Appendix B: Related NICE recommendations

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36). NICE technology appraisal guidance 130 (October 2007):

- The tumour necrosis factor alpha (TNF-α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics.
  - Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
  - Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
- TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.
- Treatment with TNF-α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.
- After initial response, treatment should be monitored no less frequently than 6-monthly intervals with assessment of DAS28. Treatment should be withdrawn if an adequate response is not maintained.
- An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.
- Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended.

- Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.
- Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
- Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

Certolizumab pegol for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 186 (February 2010)

- Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis only if:
  - certolizumab pegol is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130) **and**
  - the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200-mg syringes) free of charge to all patients starting treatment.
- When using the DAS28 (as set out in NICE technology appraisal guidance 130), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to the DAS28 and make any adjustments they consider appropriate.

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36; review of NICE technology appraisal guidance 126 and 141). NICE technology appraisal guidance 195 (August 2010)

- Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.
- Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.
- Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.
- Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.
- Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6 months after initiation of therapy. Treatment should be monitored, with

assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

- When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.
- A team experienced in the diagnosis and treatment of rheumatoid arthritis and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept.

Tocilizumab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 198 (August 2010)

- 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.
- 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.