NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Golimumab for the treatment of psoriatic arthritis

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 further information from the pivotal trial (GO-REVEAL) with regard to:

- summary data for the primary outcome

- summary data for adverse events

- details of patients' previously-received therapies

- more comprehensive efficacy data for the 100-mg treatment arm

- efficacy data from the open-label extension

- supporting evidence for the claim of a lower incidence of injection site reactions compared with TNF-inhibitors

- confirmation on when patients whose disease did not respond to golimumab switched to a higher dose

- full details on the ITT analysis

- the randomisation method, concealment of allocation, and blinding

- provide further information on the mixed treatment comparison with regard to:

- supporting evidence for the assumption that HAQ score change and PASI change are independent

- relative treatment effects of each drug compared with placebo for each outcome

- provide further information for the cost-effectiveness evaluation with regard to:

- additional sensitivity analyses

- additional cost-effectiveness acceptability curves

- model and figure corrections

- provide clarification on the cost-effectiveness data with regard to:

- interpretation of the Kyle (2005) treatment guidelines

- data sources

- the modelled dosing schedule for golimumab

Licensed indication

Golimumab (Simponi, Centocor/Schering-Plough), alone or in combination with methotrexate, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. The marketing authorisation was granted on 1 October 2009. The summary of product characteristics (SPC) notes that golimumab has also been shown to improve physical function in this patient population.

Key issues for consideration

- In Technology Appraisal 199 (Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis), the Committee concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of the TNF inhibitors in the treatment of psoriatic arthritis. The ERG for the current appraisal noted that if all TNF inhibitors are considered equally effective, etanercept, adalimumab and golimumab have comparable incremental cost-effectiveness ratios in comparison with palliative care.
    - *Can the tumour necrosis factor (TNF) inhibitors be considered as a group with the same or similar clinical effectiveness in this appraisal?*

- The efficacy outcomes for golimumab are from a single RCT of limited duration and limited sample size. There were little submitted data on the psoriasis response to golimumab treatment. Further to that, the radiographic outcomes in

the pivotal trial were evaluated at 24 weeks, which is often considered inadequate to assess radiographic changes in response to treatment.

- *Is the modelling of the long-term effectiveness of golimumab appropriate, given the short-term data available from the trial?*

- The long-term safety profile of golimumab is yet to be established. The evidence submission for the safety evaluation of golimumab was exclusively based on 14- and 24-week data from the pivotal trial for psoriatic arthritis. The manufacturer did not provide longer-term adverse event data from controlled studies of golimumab for other indications, such as rheumatoid arthritis or ankylosing spondylitis.
    - *Is it appropriate to assume that golimumab has a comparable safety profile to the other TNF inhibitors?*

- Sensitivity analyses indicate that the manufacturer's model is sensitive to changes in the assumptions about changes in HAQ score when treatment with a TNF inhibitor is withdrawn.
    - *Is it appropriate to assume that HAQ score will "rebound" by the amount equal to the original gain following withdrawal of a TNF inhibitor, or is it more appropriate to assume that some degree of treatment effect will remain?*

- The manufacturer's economic model includes a response criterion for the continuation of treatment beyond 12 weeks to the extent that a patient is modelled as coming off treatment if it has failed to produce a PsARC response at 12 weeks. Technology Appraisal 199 (section 1.3) recommends that 'treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate PsARC response at 12 weeks....'
    - *What is Committee's view on the inclusion of a response criterion in any recommendations for the use of golimumab for the treatment of psoriatic arthritis?*

- The manufacturer's model initially allowed for vial sharing of the comparator, infliximab. Following a request from the ERG, this assumption of vial sharing was removed from the model. In Technology Appraisal 199, the Committee took account of evidence that vial sharing arrangements for infliximab are available in some settings and may reduce drug wastage by up to 50%.
    - *Does the Committee consider it most appropriate to assume infliximab vial sharing or infliximab wastage in this appraisal?*

- The manufacturer performed subgroup analysis to determine the impact of golimumab treatment in people with either predominantly rheumatic or predominantly psoriatic disease. Technology Appraisal 199 recommends that for people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks, but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.
    - *Should recommendations be made in accordance with the dominant feature of the disease in this appraisal?*

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People with active and progressive psoriatic arthritis that has responded inadequately to previous DMARDs.
Intervention	Golimumab
Comparators	• Alternative TNF inhibitors • Conventional management strategies for active and progressive psoriatic arthritis that has responded inadequately to previous DMARD therapy or NSAIDs, excluding TNF inhibitors.
Outcomes	• Pain and other symptoms • Functional capacity • Effect on concomitant skin condition • Joint damage • Disease progression (using imaging, for example) • Adverse effects of treatment • Health-related quality of life.
Economic evaluation	Cost effectiveness expressed in quality-adjusted life years. Time horizon considered is lifetime of patient. Costs considered from NHS and PSS perspective. Subgroups include: • Patients with predominantly rheumatic condition • Patients with significant psoriatic condition. Sequencing of different drugs is not considered due to lack of robust evidence.

1.2 Evidence Review Group comments

1.2.1 Population

In the statement of the decision problem, the manufacturer specified the relevant population as people with active and progressive psoriatic arthritis whose disease has responded inadequately to previous DMARDs. The Evidence Review Group (ERG) reported that this exactly reflects the population specified in the NICE scope.

The manufacturer's mixed treatment comparison (MTC) included trials with patients with active and progressive psoriatic arthritis whose disease has responded inadequately to previous DMARDs. The ERG considers that all these included trials were relevant to the scope specified by NICE. However, it is noted that the trial population included patients who had received only one prior DMARD.

1.2.2 Intervention

The ERG reported that the manufacturer's evaluation of clinical efficacy and cost effectiveness adequately addressed the intervention specified in the NICE scope, although it did not specify the dose of golimumab. The manufacturer presented data on therapy initiated with golimumab 100 mg, which does not reflect the product licence. The current licensed dose of golimumab is 50 mg subcutaneously administered once a month. The licence indicates that an increase of the dose to 100 mg once a month may be considered for those patients weighing more than 100 kg who do not achieve an adequate clinical response after three or four doses. The summary of product characteristics states that continued therapy should be reconsidered in those who show no evidence of therapeutic benefit after receiving three to four additional doses of 100 mg per dose.

1.2.3 Comparators

The ERG reported that the comparators reflect exactly the NICE scope. The ERG also reported that there were no head-to-head comparisons between golimumab and the alternative TNF inhibitors. Therefore it felt that indirectly estimating the relative efficacy among the TNF inhibitors, by using a mixed treatment comparison, was an appropriate way for the manufacturer to adequately address the comparators defined in the NICE scope.

1.2.4 Outcomes

The ERG reported that in terms of the radiographic outcome, measuring radiographic changes for joint lesion response at 24 weeks is not considered adequate. Although this allows for the evaluation of the rapid onset of biological therapies, clinical advice to the ERG suggested that observing meaningful changes in joint disease through radiographic measures usually requires one year follow-up. The ERG noted that data for the health-related quality of life measure (Short Form 36 Health Survey [SF-36] at week 14) were not presented in the manufacturer's submission.

1.2.5 Economic evaluation

The ERG noted that a time horizon was not specified in the NICE scope nor in the decision problem. The ERG reported that the length of follow-up in the GO-REVEAL trial appeared to be adequate to observe the clinically meaningful changes in the efficacy outcomes of golimumab, for patients with active and progressive psoriatic arthritis. These changes included anti-inflammatory response and skin lesion response.

1.3 Statements from professional/patient groups and nominated specialists

Clinical specialists stated that psoriatic arthritis is currently treated with first-line disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, and leflunomide. Second-line treatment includes TNF inhibitors adalimumab, etanercept, and infliximab. The aim of treatment is to improve the psoriasis, arthritis, or both.

Specialists indicated that there are a number of published guidelines for the treatment of psoriatic arthritis, which include: guidelines published by the British Association of Dermatologists (Smith et al., 2009); the Group for Research and Assessment of Psoriatic Arthritis (GRAPPA; Ritchlin et al, 2009); the Scottish Intercollegiate Guidelines Network (SIGN, 2008) and the British Society for Rheumatology (BSR; Kyle et al., 2005). At the time of publication of the BSR guidelines, only etanercept was licensed for use in the UK, so this guideline is currently being updated and is expected to be completed by the end of 2010. An update of the SIGN guidelines is similarly scheduled to be published in autumn 2010.

This picture is further complicated by the fact that treatment decisions may be made by either rheumatologists or by dermatologists. However, clinical specialists indicated that patients are treated predominantly by rheumatologists in secondary care. There are no apparent clinical variations in the use of conventional DMARDs across the UK and specialists indicate that most clinicians will be confident in their use. There is, however, some variation in the availability and use of TNF inhibitor therapy, due to cost pressure and/or differing levels of expertise in the management of severe psoriatic arthritis. NHS commissioning specialists indicated that there appear to be differences of opinion between professionals as to what current practice should be

regarding the use of the TNF inhibitors, as demonstrated by the charges made to PCTs for psoriatic arthritis treatment.

Patient experts reported that psoriatic arthritis causes significant distress and psychological impact on the individual's life, employment and social activities. They reported that main impact is pain within the joints, which can hinder walking (if affecting the feet), personal care (if affecting the hands), and mobility (if affecting the large joints). Clinical specialists and patient experts indicated that the impact on a person's life from having few joints involved can be high, particularly if those joints have a significant impact on activities of daily living (such as the knees and hands.)

Patient experts and clinical specialists reported that the availability of golimumab would provide patients with greater options for treatment. Patient experts indicated a preference for the availability of golimumab as a treatment option, as it has a longer re-treatment interval (once monthly via self-injection) than adalimumab (fortnightly via subcutaneous injection), etanercept (twice weekly via subcutaneous injection) or infliximab (via 2-hour intravenous infusion at weeks 1, 2, 6 and every 8 weeks thereafter). NHS commissioning specialists indicated that this might result in a number of patients coming forward for treatment with golimumab who may have found the more frequent treatment with the other TNF inhibitors unacceptable. Commissioning specialists also noted that the availability of golimumab as an alternative with a longer interval between injections may offer the NHS reduced costs compared with infliximab, in patients who are unable to self-inject. They similarly noted the expected cost implications for those who require assistance with self-injection.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

GO-REVEAL trial data

The main clinical effectiveness data were derived from a single phase III, randomised controlled trial (GO-REVEAL) of patients. The trial compared golimumab with placebo for the treatment of active and progressive psoriatic arthritis in patients who

were symptomatic despite the use of current or previous DMARDs or nonsteroidal anti-inflammatory drugs. Of the 405 patients included in the trial, 113 were randomised to placebo, 145 were randomised to a 50 mg dose of golimumab, and 146 were randomised to a 100 mg dose of golimumab. Randomisation was maintained for 24 weeks; however, upward titration was allowed at week 16, such that patients in the placebo group could switch to 50 mg golimumab, and patients in the 50 mg golimumab group could have their dose increased to 100 mg. This dose adjustment is in accordance with the SPC for golimumab, though it should be noted that the 100 mg dose of golimumab is not directly licensed as a starting dose for the treatment of active and progressive psoriatic arthritis. In the trial, 50% of patients in the placebo group crossed over to golimumab 50 mg treatment and 20% of patients in the golimumab 50 mg group crossed over to golimumab 100 mg treatment. For the patient flow diagram of GO-REVEAL, see figure B2 (page 60) of the manufacturer's submission.

The primary outcomes in the GO-REVEAL trial were the proportion of patients achieving an American College of Rheumatology (ACR) 20 response at week 14, and the change from baseline in the psoriatic arthritis modified van der Heijde-Sharp (vdH-S) score at week 24. ACR criteria measure improvement in tender or swollen joint counts and improvement in three of the following five parameters: acute phase reactant (such as sedimentation rate); patient assessment; physician assessment; pain scale; and disability/functional questionnaire. ACR 20 response indicates the proportion of people achieving a 20% improvement in tender or swollen joint counts as well as 20 percent improvement in three of the other five criteria. The vdH-S score is used to assess erosions and joint space narrowing of joints of hands and feet in rheumatoid arthritis. The maximum possible scores are 320 for erosions, 208 for joint space narrowing, and 528 for the total score. Secondary outcomes in the direct efficacy comparisons were ACR 20 response at week 24, Psoriatic Arthritis Response Criteria (PsARC) response at weeks 14 and 24, and Psoriasis Area and Severity Index (PASI) 75 improvement at week 14 in patients with 3% or more body surface area (BSA) psoriasis at baseline. PsARC response is reported in terms of the percentage of patients achieving response according the following criteria: physician global assessment; patient global assessment; tender joint count; and swollen joint count. Overall response is defined by improvement in 2 of 4 criteria, one of which must be a joint count; there must not be worsening in any of the 4 criteria. PASI takes

values in the range from 0 (no psoriasis) to 72 (most severe). The physical functional status was measured by Health Assessment Questionnaire (HAQ) at week 24. HAQ takes continuous values in the range from 0 (no arthritis) to 3 (most severe). A negative HAQ change implies an improvement in HAQ score, as lower values of HAQ indicate less severe arthritis. The health-related quality of life was measured by the Short Form 36 Health Survey (SF-36) at week 14. The safety outcome was the incidence of adverse events.

GO-REVEAL trial results

The results of the GO-REVEAL trial are summarised below in table 1. Results for all comparable endpoints from comparator trials are presented in table 2 for comparison. The GO-REVEAL results are not those presented in the manufacturer's submission, but newly analysed intention-to-treat (ITT) results submitted by the manufacturer in response to the request for clarification (see question A10). It should be noted that analyses of PASI 50 and PASI 90 at 14 weeks and all the PASI outcomes at 24 weeks were not performed on the basis of intention-to-treat analysis. The manufacturer did not present the mean HAQ score from baseline at 14 weeks in its revised data table, though these values were originally presented in the manufacturer's submission.

The 14 week data from GO-REVEAL showed that, compared with placebo, golimumab 50 mg showed a statistically significant improvement on patients' joint disease, as measured by ACR 20 and PsARC, and on skin disease as measured by PASI 75 at both 14 and 24 weeks. There was also a significant improvement in patients' functional status (HAQ) at 24 weeks. Golimumab 100 mg achieved a similar magnitude of statistically significant treatment effects at 14 and 24 weeks.

[redacted]

The manufacturer reported that short-term radiographic measures of vdH-S score indicated that golimumab 50 mg can slow disease progression in the short term at 24 weeks with a significant reduction from baseline of 0.16 ($p = 0.01$), though this significant impact was not observed in the golimumab 100 mg group ($p = 0.09$).

Table 1 Efficacy data for golimumab in the GO-REVEAL trial

Duration	Outcomes	Golimumab 50 mg	Placebo	Relative Risk (95% CI)
14 weeks	PsARC	107/146 (73.3%)	24/113 (21.2%)	3.451 (2.49 to 4.87)
	ACR 20	74/146 (50.7%)	10/113 (8.8%)	5.727 (3.24 to 10.56)
	ACR 50	44/146 (30.1%)	2/113 (1.8%)	17.027 (4.81 to 63.32)
	ACR 70	18/146 (12.3%)	1/113 (0.9%)	13.932 (2.46 to 81.82)
	HAQ change from baseline, mean (SD)	n/a	n/a	-
	PASI 50*	63/106 (59.4%)	7/73 (9.6%)	6.198 (3.22 to 12.7)
	PASI 75*	44/109 (40.4%)	2/79 (2.5%)	15.945 (4.62 to 59.11)
	PASI 90*	22/106 (20.8%)	0/73 (0.0%)	Inf (4.21 to Inf)
24 weeks	PsARC	102/146 (69.9%)	33/113 (29.2%)	2.392 (1.81 to 3.20)
	ACR 20	76/146 (52.1%)	14/113 (12.4%)	4.202 (2.60 to 7.03)
	ACR50	47/146 (32.2%)	4/113 (3.5%)	9.094 (3.62 to 23.94)
	ACR70	27/146 (18.5%)	1/113 (0.9%)	20.897 (3.77 to 121.19)
	HAQ change from baseline, mean (SD)	0.33 ± 0.55 p < 0.001	- 0.01 ± 0.49	-
	PASI 50*	77/102 (75.5%)	6/73 (8.2%)	9.185 (4.69 to 19.45)
	PASI 75*	57/102 (55.9%)	1/73 (1.4%)	40.794 (7.86 to 232.88)
	PASI 90*	33/102 (32.4%)	0/73 (0.0%)	Inf (6.65 to Inf)
	vdH-S score change from baseline, mean (SD)	-0.16 ± 1.31 p = 0.011	0.27 ± 1.26	-

* = outcome was reported for patients with at least 3% BSA psoriasis.
N/A = not available

Table 2 Summary of results for comparator RCTs identified by the manufacturer

Trial	Duration (weeks)	Outcomes							
		PsARC	ACR 20	ACR 50	ACR 70	HAQ change from baseline	PASI 50*	PASI 75*	PASI 90*
Adalimumab									
ADEPT	**12**	2.40 (1.80, 3.20) *	4.10 (2.75, 6.14) *	9.66 (4.28, 21.79) *	32.19 (4.44, 233.11) *	-0.3 (-0.41, -0.19) **	5.00 (2.77, 9.03) *	11.33 (3.65, 35.17) *	43.00 (2.66, 696.04) *
	24	2.64 (1.93, 3.60) *	3.84 (2.59, 5.70) *	6.33 (3.34, 12.64) *	37.55 (5.21, 270.70) *	-0.30 (-0.40, -0.20) **	6.50 (3.34, 12.64) *	41.00 (5.80, 289.75) *	59.00 (3.68, 946.75) *
Genovese 2007	**12**	1.78 (1.06, 3.00) *	2.40 (1.17, 4.94) *	12.49 (1.70, 91.90) *	14.42 (0.85, 5.26) ns	-0.2 (-0.36 ,-0.04) *	-	-	-
	24 (OLE)	NR	NR	NR	NR	NR	-	-	-
Etanercept									
Mease 2000	**12**	3.71 (1.91, 7.21)	5.50 (2.15, 14.04)	15.00 (2.11, 106.49)	9.00 (0.51, 160.17)	N/A	2.00 (0.72, 5.53)	11.00 (0.65, 186.02)*	-
Mease 2004	**12**	2.35 (1.72, 3.21) **	3.86 (2.39, 6.23) **	9.78 (3.62, 26.41) **	23.68 (1.41, 396.53) **	-	-	-	-
	24	3.05 (2.10, 4.42) **	3.68 (2.17, 6.22) **	9.52 (3.52, 25.75) **	9.27 (1.20, 71.83) *	47.20 (32.47 , 61.93) **	2.65 (1.46, 4.80) **	7.05 (1.68, 29.56) **	1.88‡ (0.36, 9.90)

Infliximab									
IMPACT	**14**	5.71 (2.82, 11.57)	5.83 (2.68, 12.68)	19.00 (2.64, 136.76)	23.00 (1.39,380.39)	-	-	-	-
	16	3.55 (2.05, 6.13) *	6.80 (2.89, 16.01) *	49.00 (3.06, 504.86) *	31.00 (1.90, 504.86) *	-51.4 (-74.5, 28.3) *	33.26 (2.17, 510.71)	22.91 (1.47, 356.81)	12.57 (0.78, 203.03)
IMPACT2	**14**	2.85 (2.03, 4.01)	5.27 (2.95, 9.44)	12.00 (3.82, 37.70)	15.00 (2.02, 111.41)	-67.00 (-86.66, -47.33)	-	-	-
	24	2.19 (1.60, 3.00)	3.38 (2.08, 5.48)	10.25 (3.81, 27.55)	13.5 (3.30, 55.26)	-65.40 (-87.20, -43.60)	-	-	-

Note that all arthritis outcomes (PsARC, ARC20/50/70) are irrespective of background methotrexate use. All results reported as changes from baseline (HAQ) are given as "mean (standard deviation)"; all others are given as "relative risk (95% credible interval)". For the adalimumab trials, PASI scores are given for patients with ≥3% body surface area psoriasis; PASI scores for the infliximab trials are for patients with PASI scores ≥2.5 at baseline. ns indicates 'not significant'; * indicates p≤0.05; ** indicates p≤0.001; N/A indicates not available; NR indicates not reported; ‡ indicates annualised rate of progression, rather than change from baseline.

Mixed treatment comparison

In the absence of head-to-head comparisons between golimumab and the alternative TNF inhibitors, the manufacturer conducted a mixed treatment comparison. The manufacturer's MTC analyses included seven trials evaluating golimumab, plus the three alternative TNF inhibitors (etanercept, infliximab and adalimumab). These trials (summarised in table B2 on page 29 of the manufacturer's submission) included: the GO-REVEAL trial (golimumab versus placebo); two RCTs (Mease 2000 and Mease 2004) comparing etanercept with placebo; two RCTs (IMPACT and IMPACT2) comparing infliximab with placebo; and two RCTs (ADEPT and Genovese 2007) comparing adalimumab with placebo. All of the TNF inhibitors are licensed for the treatment of patients with active and progressive psoriatic arthritis whose disease has inadequately responded to previous DMARDs.

The population characteristics of all seven trials are summarised and compared in table 4.5 of the ERG report. The trials are similar in terms of patients' joint disease severity at baseline (for example, mean tender joint count, mean swollen joint count). There were, however, differences in terms of the proportions of patients that could be evaluated for psoriasis endpoints at baseline between included trials.

The outcomes of interest in the manufacturer's mixed treatment comparison analyses were PsARC response, change in HAQ score given PsARC response to treatment, and change in PASI in patients with BSA 3% or above at baseline. The manufacturer selected absolute PASI change as its main outcome (using the last available endpoint), stating that this was the most appropriate outcome for the economic modelling. No analysis was undertaken on the ACR outcomes. For PsARC response the manufacturer's submission model used a fixed effect meta-analysis, which incorporated 12 or 14 week outcome data. HAQ conditional on a PsARC response was modelled using two linked meta-analyses. The meta-analyses estimated the probability of response and then the mean reduction in HAQ score conditional on that response. An overview of the evidence synthesis model is provided in table 4.2 of the ERG report.

Table 3 below (adapted from table 4.6 of the ERG report) presents the results of the manufacturer's MTC analyses, all of which feed into the economic model. Based on the results of MTC analyses, the manufacturer states that the efficacy of golimumab is comparable to other TNF inhibitors including infliximab, adalimumab and etanercept. The ERG, however, noted the following a number of differences. Infliximab is associated with the highest probability of arthritis response according to PsARC criteria and the highest improvement in psoriasis according to absolute change in PASI from baseline. However, it ranks 2nd, behind etanercept, for functional status (measured by HAQ) for both those whose disease responded to treatment based on PsARC score, and those whose disease did not respond. Golimumab was associated with the third highest PsARC response and absolute change in PASI from baseline. Golimumab had the lowest HAQ change from baseline for both for both those whose disease responded to treatment based on PsARC score ([redacted]), and those whose disease did not respond ([redacted]). For all four anti-TNF agents, the changes in HAQ for those patients who did not achieve a PsARC response were [redacted].

Table 3 Results of the MTC analyses in the manufacturer's submission

Outcomes	**PsARC response** Mean (SD) [95% Credibility Interval]	**HAQ changes from baseline in those with PsARC response** Mean (SD) [95% Credible Interval]	**HAQ changes from baseline in those without PsARC response** Mean (SD) [95% Credible Interval]	**PASI change from baseline in patients ≥3% BSA psoriasis at baseline** Mean (SD) [95% Credible Interval]
Placebo				
Result	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab				
Result	[redacted]	[redacted]	[redacted]	[redacted]
Rank	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept				
Result	[redacted]	[redacted]	[redacted]	[redacted]
Rank	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab				
Result	[redacted]	[redacted]	[redacted]	[redacted]
Rank	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab				
Result	[redacted]	[redacted]	[redacted]	[redacted]
Rank	[redacted]	[redacted]	[redacted]	[redacted]

KEY: PsARC response: Estimate from the manufacturer's mixed treatment comparison (MTC) of the mean probability that a patient will respond to biological treatments (or palliative care), according to PsARC criteria, at 12-weeks. HAQ change from baseline in those with PsARC response: Measures the absolute change in HAQ score from baseline for those patients whose disease has responded to biological treatment (or palliative care), according to PsARC criteria, at 12-weeks. HAQ change from baseline in those without a PsARC response: Measures the absolute change in HAQ score from baseline (natural history) for those patients whose disease has not responded to biological treatment (or palliative care), according to PsARC criteria, at 12-weeks. PASI change from baseline: Measures the absolute change in PASI score from baseline for those with measurable psoriasis (≥3% Body Surface Area). A negative PASI change implies an improvement in psoriasis symptoms. Note that PASI changes were not differentiated by PsARC response in the manufacturer's MTC, as independence between the two outcomes has been assumed.

Safety evaluation

The discussion of adverse effects in the manufacturer's submission comprised a summary of adverse effects from the GO-REVEAL trial and a table of summary information from six systematic reviews (see tables B17 and B18, pages 90 and 91 of

the manufacturer's submission). Only data up to week 24 from GO-REVEAL were presented. The longer-term follow-up safety data (at 52 and 104 weeks) from the GO-REVEAL trial were not available.

The limited available evidence for the safety evaluation from the single GO-REVEAL trial suggested that the most frequently reported adverse events associated with golimumab therapy were infections and infestations, upper respiratory tract infection and nasopharyngitis. The manufacturer's submission stated that serious adverse events, including serious infection and malignancy, were rare (n = 5). No active tuberculosis in any treatment arm was observed. For details of adverse events across the randomised groups in GO-REVEAL, see table B17 (page 90) of the manufacturer's submission.

On the basis of the safety evaluation results from the GO-REVEAL trial, the manufacturer concluded that golimumab is a safe treatment option similar to other TNF inhibitors.

2.2 Evidence Review Group comments

GO-REVEAL trial

The ERG reported that the main limitation of the efficacy evaluation of golimumab is that there were limited efficacy data available. The analyses for efficacy outcomes were limited to only one RCT (GO-REVEAL) with limited sample size. In particular, few patients provided data on the psoriasis response to golimumab treatment. The ERG reported that overall there was baseline comparability of joint disease severity between the treatment and placebo groups.

The ERG indicated that the ACR 20 appeared to be appropriate as the primary outcome. The ERG reported that ACR 20 is generally accepted to be the minimal clinically important difference that indicates some response to a particular treatment.. The change from baseline in the psoriatic arthritis modified van der Heijde-Sharp score at week 24 was also used as the primary outcome for radiographic assessment in the GO-REVEAL trial. The ERG reported that this radiographic scoring method has not been validated in large psoriatic arthritis populations. The ERG indicated that measuring radiographic data on progression of joint disease at 24 weeks is a short

time over which to identify a clinically significant effect of treatment, and that at least one-year follow-up is considered necessary.

Overall, the analyses on the 14 week data in the GO-REVEAL trial were considered reliable. Longer-term data suggested that the treatment effects were maintained in those who continued therapy or had an increase in the dose of golimumab from 50 mg to 100 mg. However, the ERG noted there was lack of the robustness for the analyses on the 24 week data in terms of the beneficial effect of golimumab therapy relative to placebo. This is because the analyses failed to adjust the treatment contamination due to patients' crossing-over. In the trial, 50% of patients in the placebo group crossed over to golimumab 50 mg treatment and 20% of patients in the golimumab 50 mg group crossed over to golimumab 100 mg treatment. While the analyses at 24 weeks involved all the intention-to-treat data (that is, they included these crossing-over data) from the randomisation, it appears that these intention-to-treat analyses failed to adjust for the treatment contamination due to patients' crossing-over at week 16. Therefore, the failure to adjust this treatment contamination in the analyses may have threatened the internal validity of trial results for all the outcomes at 24 weeks.

The ERG had noted that the intention-to-treat analysis was not adequately applied in the efficacy analysis in the manufacturer's submission. It requested that such analyses presented in the manufacturer's submission were clarified. In the clarification responses provided by the manufacturer, the intention-to-treat analysis was appropriately performed for most efficacy outcomes. Given the evidence that treatment effect was maintained during the follow-up in the trial, it was considered appropriate to have used the last observation carried forward method to impute missing data. However, it should be noted that analyses of PASI 50 and PASI 90 at 14 weeks and all the PASI outcomes at 24 weeks were not performed on the basis of intention-to-treat analysis. Therefore, these analyses may have potentially compromised the reliability of the results in terms of skin disease outcomes.

Mixed treatment comparison

Based on references provided in response to clarification (clarification response A12), the ERG considered that all relevant studies had been included in the evaluation of direct trial evidence of the efficacy of golimumab and MTC analyses. The included trials were generally of good quality. Randomisation, blinding, concealment of allocation and intention-to-treat analyses were adequate in most trials. All four TNF inhibitors being evaluated in the included trials had a common comparator of placebo, allowing the network between golimumab, etanercept, infliximab and adalimumab to be established. Thus, the MTC network in the manufacturer's submission was appropriately constructed. Overall, the ERG considered that there was a reasonable degree of clinical heterogeneity between the included trials in terms of joint and skin disease severity and functional status. Therefore, the assumption of exchangeability between the trials for the purposes of the MTC was acceptable.

The ERG noted that the majority of patients had previously received only one DMARD. No trial specified the failure to respond to at least two DMARDs as a recruitment criterion. Only patients who meet this recruitment criterion are considered as eligible for the biological treatment under the current BSR guidelines and NICE guidance for etanercept, infliximab and adalimumab (technology appraisal 199). Thus, the trial participants in the MTC analysis were likely to have less severe psoriatic arthritis compared to those patients receiving biological treatment in routine practice. Given this consideration, trial participants were not precisely representative of the active and progressive psoriatic arthritis population recommended for TNF inhibitors under the current guidelines. The ERG commented that it remained unclear about the extent to which the beneficial effects observed in these trial participants in the MTC analysis were similar in those treated in routine clinical practice.

The ERG noted that all included trials except for Mease (2000) used ACR 20 response as the primary outcome. These trials were often powered to detect a significant difference between treatment groups for this outcome. See table B2 in the manufacturer's submission for a list of the included RCTs. However, the manufacturer's MTC analysis did not include the outcome of ACR 20. In addition, PASI was chosen as the primary measure of skin disease response in the MTC. The

ERG considered this outcome to be an appropriate measure for the skin disease response, as recommended by the British Association of Dermatologists (BAD) guidelines.

Safety evaluation

The ERG had concerns with the data presented for the safety evaluation in the manufacturer's submission. The inclusion/exclusion criteria in the submission for the evaluation of safety did not appear to correspond with the synthesis of safety data presented. Furthermore, the incidence of serious adverse events was not adequately reported. The manufacturer failed to consider adverse event data for golimumab from controlled studies with other conditions such as rheumatoid arthritis and ankylosing spondylitis. Given these limitations and uncertainties, the ERG reported that the manufacturer's conclusion that golimumab is a safe treatment option similar to other TNF inhibitors may be premature and may not be reliable.

2.3 Statements from professional/patient groups and nominated specialists

Clinical specialists reported that the Psoriatic Arthritis Response Criteria (PsARC) are most often used to assess the efficacy of treatment. Specialists report that patients with few joints involved are poorly served by the assessment tool, as it is better suited for those with polyarthritis. They noted that this bias of the PsARC towards use in polyarthritis is reflected in the patient characteristics of the pivotal trial for golimumab.

Patient experts and clinical specialists indicated that there may be disadvantages associated with the use of golimumab with respect to adverse effects and its long-term safety profile. The trial suggests that the safety profile is similar to that of the other TNF inhibitors. Clinical specialists made specific reference to the rare but serious demyelinating diseases associated with long-term administration of TNF inhibitors.

Clinical specialists stated that the use of this technology should be supervised in specialist clinics in secondary care. They indicated that it is likely that golimumab is

sufficiently similar to the other biological agents available for the treatment of psoriatic arthritis that, if NICE were to recommend golimumab, there would be little effect on the delivery of care to patients with psoriatic arthritis. This is because the resources needed support this medication should already be in place (specialist clinics, specialist nurses/allied health professionals, national delivery and support services). NHS commissioning specialists reported that any training arrangements for etanercept self-injection should be relevant for golimumab.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer conducted a literature search to identify published cost-effectiveness studies for TNF inhibitors in the treatment of psoriatic arthritis. Five cost-effectiveness analyses were identified. Details of these five cost-effectiveness evaluations were summarised in the manufacturer's submission (pages 99–110) and quality assessed (pages 196–204, appendix 11). The cost effectiveness analyses included the model submitted for the appraisal of adalimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 125), the model submitted for the appraisal of infliximab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 104), the Assessment Group model for the multiple technology appraisal of etanercept, infliximab and adalimumab (NICE technology appraisal guidance 199), and two published models (Bravo Vergel at al [2007] and Bansback et al [no reference provided]).

In addition to identifying the published evaluations, the manufacturer developed a *de novo* economic model. An overall summary of the manufacturer's approach and signposts to the relevant sections in the manufacturer's submission are reported below in table 5.1 of the ERG report.

Model structure

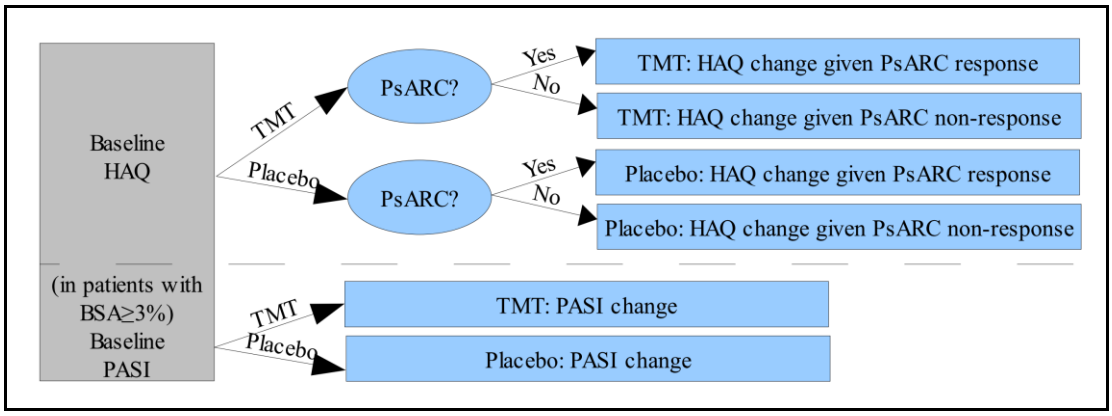
The intervention evaluated in the manufacturer's model is golimumab 50 mg (once a month). Golimumab is compared with the following treatment alternatives:

- Infliximab: 5 mg/kg given as an intravenous infusion over a 2 hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter;
- Adalimumab: 40 mg administered every other week as a single dose via subcutaneous injection;
- Etanercept: 25 mg administered twice weekly, or 50 mg administered once weekly; and
- Palliative care comprising DMARDs.

The patient cohort within the model was those with active and progressive psoriatic arthritis whose disease had responded inadequately to DMARDs. The model structure in terms of the cohort flow is represented by figure 1 below (reproduced from the manufacturer's response to clarification question B1).

The model captured response to treatment using HAQ score (as the arthritis outcome) and PASI score (as the psoriasis outcome). The model predicted a change in HAQ conditional on PsARC response. This is illustrated below in figure 1, reproduced from figure B9 in the manufacturer's submission.

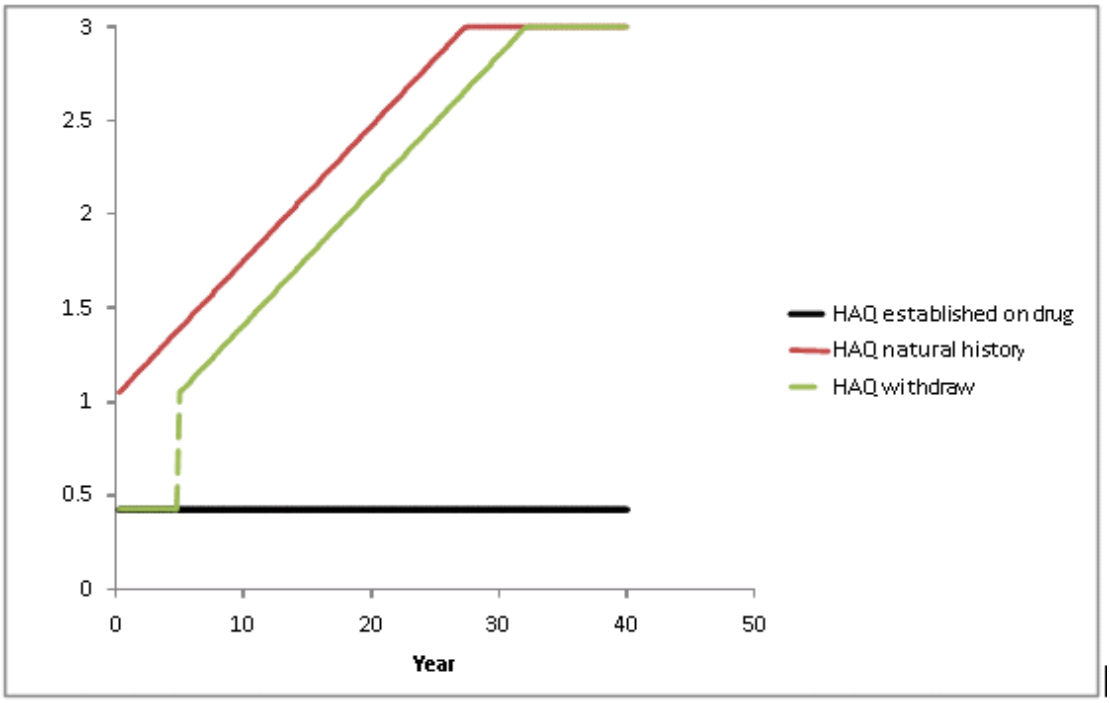
Figure 1 Clinical effectiveness model structure (modelled outcomes are shaded in blue)



The manufacturer describes the model as having a first cycle of 0–12 weeks, a second cycle of 13–24 weeks, and annual cycles thereafter. At 12 weeks, if treatment had produced a PsARC response, a patient stayed on treatment. A reduction

(improvement) in HAQ for the first 3 cycles (12 weeks, 24 weeks and 52 weeks) was assumed, after which, HAQ for those whose disease responds to treatment was assumed to remain constant. If, at 12 weeks, treatment failed to achieve a PsARC response, the patient came off treatment. The HAQ change for those whose disease does not respond was only applied for the first cycle, after which it was assumed that the patient withdrew from biological therapy and followed a natural history rate of progression (worsening) of HAQ (0.0719 per year taken from the Assessment Group's model for technology appraisal 199). For patients in whom treatment had achieved a PsARC response, a one-off improvement in PASI score was modelled. For a patient who does not start biologic therapy and instead receives palliative care, HAQ score increases (worsens) overtime in line with natural history (see figure 2 below).

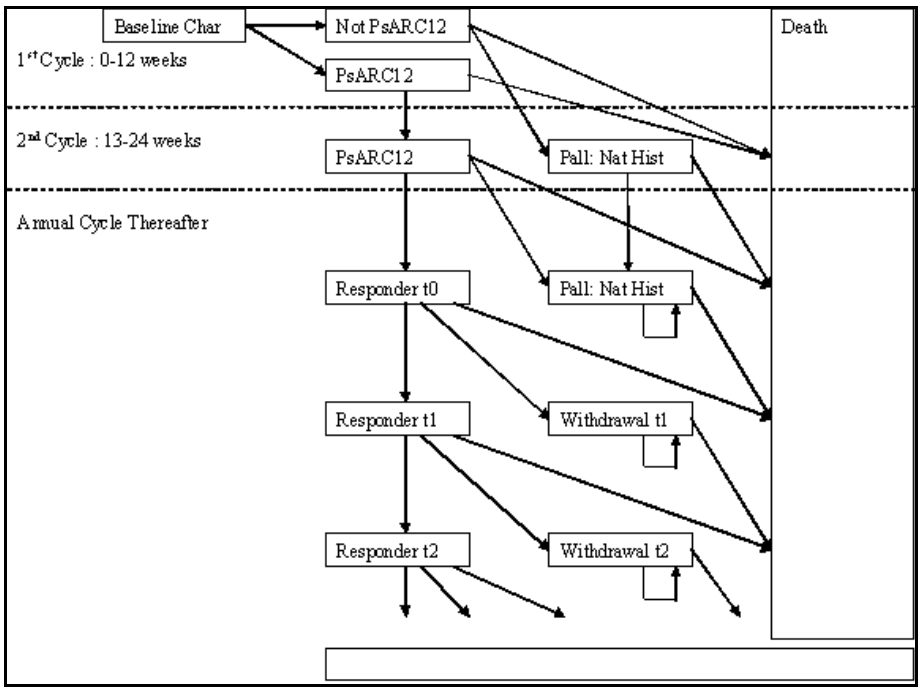
Figure 2 Illustration of the progression of psoriatic arthritis measured by HAQ in the model for patients who (i) are established on biological therapy (ii) never start biological therapy (iii) withdraw from biological therapy after 5 years



Patients were assumed to have the same baseline characteristics as those observed in the GO-REVEAL trial. Estimates of responses to treatment were derived from the mixed treatment comparison. The HAQ reductions for the second and third cycles

appear to have been derived from the open label follow-up period of patients in the GO-REVEAL trial; however, this was not explicit in the manufacturer's submission (see page 116) and clarification was sought. For those whose disease did not respond to treatment with according to PsARC at 12 weeks, the manufacturer's submission stated that the golimumab RCT showed that PASI response was independent of PsARC response. The same lack of association between PASI and PSARC responses was assumed for all treatments. The model structure in terms of the cohort flow is represented by figure 3 below (reproduced from the manufacturer's response to clarification question B1).

Figure 3 Diagrammatical representation of the manufacturer's model structure



Annual withdrawals from treatment were taken from Assessment Group's model for technology appraisal 199 ('Etanercept, infliximab and abatacept for the treatment of psoriatic arthritis'; 16.5% per annum). The same withdrawal rate was applied to all treatment strategies. After withdrawal, patients are assumed to go onto palliative care in the base-case model. HAQ score "rebounds" (quickly increases) to the baseline level and then increases at the same rate as those who never started on biologic therapy (as shown in see figure 2). After withdrawal, PASI also rebounds to baseline

level and then remains unchanged. The manufacturer's model used UK life tables along with psoriatic arthritis-specific mortality multipliers to estimate mortality. The same mortality rate was assumed for all treatments and for no treatment (that is, there was no differential impact of the alternative therapies on mortality). Adverse events were not included in the analysis.

The primary outcome used in the modelling was quality-adjusted life years, estimated as a function of both HAQ and PASI. An evidence synthesis model was used to determine the probability of PsARC response to anti-TNF agents at around 12 weeks, the associated HAQ for PsARC responders and non-responders, and the average change in PASI from baseline, for each biological drug. The manufacturer stated that the use of PsARC accords with NICE and BSR guidelines, and is widely accepted as an appropriate outcome to assess response in psoriatic arthritis.

The manufacturer adjusted for 'the placebo effect' by subtracting the mean HAQ change in the placebo group (across PsARC responders and non-responders) from the HAQ change of patients on biological therapy.

In the base-case model, a decision is made to continue or withdraw from TNF inhibitors according to PsARC response at 12 weeks. In addition to the 12 week PsARC response decision rule, the model was constructed with the flexibility to allow a 24 week decision rule. For a more detailed description of the model, see section 6.2 of the manufacturer's submission.

Model inputs: utilities

In the base case, an algorithm estimating the utilities based on HAQ and PASI used in the Assessment Group's model for technology appraisal 199. A separate regression analysis using patient level data from the GO-REVEAL trial was used to predict 'utility' from HAQ and PASI scores. Two alternative methods to generate values for the utilities were explored: the Gray algorithm (selected as the base case) and the Brazier algorithm (see pages 129–135 of the manufacturer's submission). The Gray algorithm converts SF-36 to EQ-5D health states and then to utilities, whereas the Brazier algorithm estimates utilities directly from SF-36.

Model inputs: costs

The costs used in the model are summarised in table 5.3 of the ERG report (contains commercial-in-confidence information). Resource use associated with treatment, administration and monitoring of infliximab, etanercept and adalimumab was taken from the Assessment Group's model for technology appraisal 199. The manufacturer assumed that the annual acquisition cost (including administration and monitoring) of golimumab (50 mg once per calendar month) was £9294.96 (which is comparable to that of adalimumab). The British National Formulary (BNF) was used to cost other medications. Costs for infliximab were calculated assuming that vial sharing was allowed (3.5 vials).

Results

The base-case results of the model are presented in table 4 below (reproduced from table 6.6 in the ERG report). Please note that these are not the results presented in the manufacturer's submission. The ERG reported that the manufacturer did not correctly calculate the ICERs, as they did not exclude extendedly dominated alternatives. According to the manufacturer's model, with the ICERs re-calculated, golimumab, adalimumab and infliximab are all either dominated or extendedly dominated by etanercept.

Table 4 Base case results in the manufacturer's submission, re-calculated by the ERG

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)*	Incremental QALYs*	ICER versus Palliation (£/QALY)	ICER incremental vs TNF inhibitors** (£/QALY)
Palliation	£62,224	6.61	-	-	-	-
Adalimumab	£86,410	7.89	£24,186	1.28	£18,824	Extendedly dominated
Golimumab	£94,151	8.21	£7,740	0.31	£19,993	Extendedly dominated
Etanercept	£94,578	8.49	£428	0.29	£17,177	£17,209
Infliximab	£106,620	8.49	£12,042	0.00	£23,578	Dominated

* = difference between the treatment and the lower ranked alternative, without considering extended dominance

** = difference between the treatment and the next best alternative, excluding extended dominated strategies

A sub-group analysis was conducted based on the patients presumed to have predominantly rheumatic disease. Another subgroup analysis was conducted including only those patients with significant psoriasis. Please note that these are not the results presented in the manufacturer's submission. The ERG reported that the manufacturer did not correctly calculate the ICERs, as they did not exclude extendedly dominated alternatives. The ERG-re-calculated results of the subgroup analyses are shown in tables 5.1 and 5.2 (reproduced from tables 5.12 and 5.13 of the ERG report).

Table 5.1 Results of the 'rheumatic patients only' subgroup analysis, as re-calculated by the ERG

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Palliation	£40,275	5.85			-
Adalimumab	£66,377	7.35	£26,102	1.50	ED
Golimumab	£74,542	7.71	£8,165	0.36	ED
Etanercept	£74,767	8.06	£225	0.35	£15,607
Infliximab	£81,990	8.04	£7,223	-0.03	Dominated

Note: ED = extendedly dominated

Table 5.2 Results of the 'significant psoriasis patients only' subgroup analysis, as re-calculated by the ERG

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Palliation	£70,342	5.30			-
Adalimumab	£93,820	6.83	£23,478	1.54	ED
Golimumab	£101,403	7.21	£7,583	0.37	ED
Etanercept	£101,906	7.55	£503	0.35	£14,028
Infliximab	£107,608	7.56	£5,702	0.01	£570,200

Note: ED = extendedly dominated

Univariate and probabilistic sensitivity analyses were also undertaken by the manufacturer. These are described in full on pages 145–146 and 150–151 of the manufacturer's submission, though it should be noted that these, as with the base

case results, did not exclude extendedly dominated alternatives. The results of the probabilistic sensitivity analysis were presented using a cost-effectiveness acceptability curve, showing the probability that each treatment strategy is the most cost-effective at various values for the cost-effectiveness threshold. The ERG-re-calcualted the cost-effectiveness acceptability curve (figure 6.1, page 73 of the ERG report) indicates that the probability of golimumab being cost effective was almost zero at all values of the willingness-to-pay threshold.

The ERG asked the manufacturer to carry out an additional sensitivity analysis that took into account the Committee's decision in a previous appraisal of TNF inhibitors for psoriatic arthritis, which assumed an equal clinical effectiveness for all TNF inhibitors. The results are presented below in table 6 (reproduced from table 6.7 in the ERG report).

Table 6 Results assuming equal clinical effectiveness for all TNF inhibitors

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus palliation (£/QALY)
Palliation	£62,224	6.61	-	-	-
Adalimumab OR Golimumab	£92,877	8.59	£30,653	1.98	£15,494
Etanercept	£92,879	8.59	£2	0	£15,495
Infliximab	£104,401	8.59	£11,522	0	£21,319

3.2 Evidence Review Group comments

Model

The ERG considered the baseline characteristics (age, patient weight, HAQ, PASI and proportion with psoriasis) to be appropriate for this population. The model uses a homogeneous cohort of patients considered representative of the groups of patients eligible for biological therapies to treat psoriatic arthritis – that is, patients whose condition has failed to respond to two or more conventional DMARDs. Because of this, the ERG reported that there is a possibility that the likely treatment option would

be palliative care. However, palliative care may consist of no therapy rather than further DMARDs. The ERG reported that the use of DMARDS to represent palliative care may have the potential to artificially inflate the cost effectiveness of TNF inhibitors as, in practice, DMARDs are liable to be more effective than palliative care.

The ERG reported that the model structure was reasonable, as were the assumptions regarding withdrawals and mortality. The ERG noted that HAQ progression while not on biological therapy (also called natural history progression) is estimated using the Leeds cohort study data. The Leeds dataset is, however, small, including only 24 patients. In addition, patients surveyed do not meet the requirements for this analysis, in that their condition has not failed to respond to treatment with at least two previous DMARDs. The ERG stated that it is also not clear if patients met the current guideline criteria for initiating anti-TNF agents for psoriatic arthritis (three tender and three swollen joints).

With regard to the assumption of a placebo effect, the ERG reported that palliative care was actually DMARDs (an active treatment), which may have led to an overestimation of the effectiveness of TNF inhibitors. This overestimation is likely to be small, and given that the same adjustment is applied to all TNF inhibitors, is unlikely to bias the comparison between TNF inhibitors. It may, however, affect the comparison with palliative care.

The ERG noted that the manufacturer's model included an additional 4 hours of staff nurse costs, apparently to cover training patients to self-administer subcutaneous TNF inhibitors. The ERG considered that this may be unnecessary (that is, double-counting) and requested further justification for this assumption. The ERG thought that all other costs used within the manufacturer's submission model were appropriate.

If no response is achieved at 12 weeks, the license allows a higher dose of 100 mg per administration, for patients weighing over 100 kg. A number of patients switched to a higher dose of golimumab in GO-REVEAL when their condition did not respond at a lower dose. Therefore the ERG considered that it may have been appropriate to have included this scenario in the sensitivity analysis. Further analysis on this issue

was requested from the manufacturer but they stated that suitable data were not available to model this option.

Analyses

Some subgroup analysis was undertaken on the impact of TNF inhibitors on patients with predominately rheumatic disease and a subgroup of patients with significant psoriasis. The ERG reported that these analyses seemed appropriate, given that psoriatic arthritis can have variable impact on both the joint and skin component of the disease.

The manufacturer undertook a detailed set of scenario analyses and probabilistic sensitivity analysis. However, the ERG considered that parameter uncertainty was not fully explored. This is because not all relevant parameters seem to have been considered uncertain in PSA (see table 5.7 of the ERG report). The ERG considered this to prevent any correct characterisation of the uncertainty associated with the model.

Results

The ERG reported that the manufacturer did not correctly calculate the ICERs used to compare the cost effectiveness of the treatments. The manufacturer did not exclude extendedly dominated alternatives. The re-calculated base case (table 4) and sub-group (tables 5.1 and 5.2) results are presented above in section 3.1.

The re-calculated cost-effectiveness acceptability curve is presented in figure 6.1 of the ERG report. This curve indicates that the probability that golimumab is cost effective is almost zero at all values of the cost-effectiveness threshold. This is consistent with the result in the deterministic model that golimumab is extendedly dominated by etanercept.

The ERG was the Assessment Group for the recent Multiple Technology Appraisal of etanercept, infliximab and adalimumab for psoriatic arthritis (technology appraisal 199). During that appraisal, the Assessment Group constructed a new decision model to compare the cost effectiveness of these anti-TNF agents against each other

and palliative care. Further analyses were conducted using both the manufacturer's model and the ERG model previously developed by York Assessment Group during the recent appraisal of etanercept, infliximab and adalimumab. Both models have a broadly similar structure and data and give similar results, indicating that golimumab is extendedly dominated by etanercept. Sensitivity analyses did not change these conclusions.

4 Equalities issues

No equality and diversity issues were identified at this stage of appraisal.

5 Authors

Whitney Miller, Bhash Naidoo and Helen Knight, with input from the Lead Team (Christopher Cooper and Katherine Payne).

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 Centre for Reviews and Dissemination/Centre for Health Economics Technology Assessment Group (University of York):

- Yang H, Epstein D, and Bojke L, et al., Golimumab for the treatment of psoriatic arthritis, August 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Schering-Plough Ltd

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

- NHS Cambridgeshire (on behalf of NHS Havering)
- British Association of Dermatologists
- British Society for Rheumatology
- Psoriasis and Psoriatic Arthritis Alliance
- Royal College of Pathologists
- Primary Care Rheumatology Society

C Additional references used:

Kyle S, Chandler D, Griffiths CE, et al (2005) Guideline for anti-TNF therapy in psoriatic arthritis. Rheumatology, 44: 390-397.

Ritchlin CT, Kavanaugh A, Gladman DD et al (2009) Treatment recommendations for psoriatic arthritis, Annals of the Rheumatic Diseases, 68:1387-1394.

Rodgers M, Epstein D, Bojke L, et al (2009) Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation, CRD/CHE Technology Assessment Group, University of York.

Smith CH, Anstey AV, Barker JNWN, et al (2009) British Association of Dermatologists' guidelines for biologic interventions for psoriasis. British Journal of Dermatology, 161: 987–1019.

Technology Appraisal No.199, August 2010, Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Expected review date June 2013.