NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Golimumab for the treatment of psoriatic arthritis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
The British Society for Rheumatology	BSR feel that all of the relevant evidence has been taken into account.	Comment noted. No action required.
The British Society for Rheumatology	BSR do not agree that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. There is not sufficient evidence to consider that golimumab is in any way different to the other anti-TNF drugs in use and recommended for the treatment of psoriatic arthritis. Part of the economic analysis relies on the manufacturers' recommendation that 100mg doses be used in patients over 100kg that show an inadequate clinical response to 50mg monthly. However, the clinical experts present at the appraisal indicated that they would not prescribe golimumab on this basis but would consider switching to another anti-TNF agent.	The Committee heard from the clinical specialists that they would probably use to a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6). The Committee considered the evidence of comparative clinical effectiveness in light of comments received on the ACD. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Consultee	Comment	Response
The British Society for Rheumatology	The provisional recommendations are not sound or a suitable basis for guidance to the NHS. In view of above the committee should reconsider the decision. It may be prudent to ask the manufacturer to provide more data on safety of golimumab in other indications and to provide more long term data on the efficacy and safety for this indication.	Following consultation on the Appraisal Consultation Document, the Committee considered additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD sections 3.8 and 4.10). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
The British Society for Rheumatology	There are no equality-related issues that need special consideration and are not covered in the appraisal consultation document.	Comment noted. No action required.

Consultee	Comment	Response
The British Society for Rheumatology	Overall, the manufacturer should be able to supply some extra information to address the gaps in data presented to the committee. However, based on the evidence presented there is no reason not to support golimumab's use alongside the other three agents already approved? It will provide patients with a further agent that could give them significant benefit.	Following consultation on the Appraisal Consultation Document, the Committee considered additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD sections 3.8 and 4.10). The Committee considered the evidence of comparative clinical effectiveness in light of comments received on the ACD. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
The Psoriasis and Psoriatic Arthritis Alliance	As an organisation that represents people affected by psoriasis and psoriatic arthritis, we always welcome the development of new therapies for these conditions, and the subsequent availability within the NHS, but only if the evidence is robust and the risk benefit profile is justifiable. We are also mindful that the cost of treatments to the NHS must also be considered.	Comment noted.
The Psoriasis and Psoriatic Arthritis Alliance	In our original submission we could only identify the manufacturers GO-REVEAL study, which forms the efficacy evidence, so therefore believe that there isn't any other evidence which could have been used.	Comment noted. No action required.
The Psoriasis and Psoriatic Arthritis	It is a concern to us that given the length of availability of other similar agents and subsequent NICE approval, the manufacturer has not considered head–to-head	Comment noted.

Consultee	Comment	Response
Alliance	trials with etanercept and therefore has made it difficult to rank the treatment. There also appears to have been some difficulty in gaining indirect comparative data, which again, is a disappointment.	
The Psoriasis and Psoriatic Arthritis Alliance	From a patient perspective, when given choice of treatment, it would-be useful if trials were reflective of the eventual clinical scenario, and therefore designed to meet the eventual need.	Comment noted.
The Psoriasis and Psoriatic Arthritis Alliance	Making a decision on which course of treatment to take for a chronic disease is never easy, but if the evidence is poor and long-term safety profiles are unknown, the choice is even harder, and unsatisfactory to both patient and family, as adverse outcomes might affect quality of life.	Comment noted. Following consultation on the Appraisal Consultation Document, the Committee considered additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD sections 3.8 and 4.10). The Committee understood, from the information provided by the clinical and patient experts, the impacts of the disease on quality of life (see FAD section 4.2).
The Psoriasis and Psoriatic Arthritis Alliance	Based on the ACD the cost of each drug, including the agents which are already available appear similar in price and have relative effectiveness, if golimumab was available and based on the cost indicated it would be ranked behind existing agents and the likelihood of it being used might be low, so impact on budgets might also be low.	The Committee does not base its decision on the potential budget impact of a technology. The Committee takes account of how its advice may enable the more efficient use of available healthcare resources, as represented by estimates of incremental cost effectiveness (see Guide to the Methods of Technology Appraisal, section 6.2.14).

Consultee	Comment	Response
The Psoriasis and Psoriatic Arthritis Alliance	If data was able to help identify which patient is more likely to benefit from the use of any of the agents, although the cost, might be higher relative benefit or lack of benefit might make the treatment more cost effective, as it would be known which treatments will not work. If further research was carried out to ascertain such knowledge then this might make patients more likely to be prescribed a particular agent without the subsequent need to fail.	The Committee considered the evidence of comparative clinical effectiveness in light of comments received on the ACD. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
The Psoriasis and Psoriatic Arthritis Alliance	Looking at the submissions from the clinical experts, it is concerning to see reported that psoriasis was triggered or exacerbated in people given anti-TNF drugs, which would need to be a consideration in prescribing as this if severe, could impact adverse event utility costs.	The summary of product characteristics (SPC) for golimumab reports that the most common adverse reactions are upper respiratory tract infections, including nasopharyngitis, pharyngitis, laryngitis and rhinitis. For full details of adverse effects, contraindications, special warnings and precautions for use, see the SPC. The Committee considered the evidence on the adverse event rates associated with the use of golimumab, and the additional evidence submitted by the manufacturer on the long-term adverse event data for golimumab in people with psoriatic arthritis, and also for people with rheumatoid arthritis and ankylosing spondylitis. It concluded that although there remains uncertainty about golimumab's long-term adverse event profile, it had not been shown to be different from that of other TNF inhibitors (see FAD section 4.10).

Consultee	Comment	Response
The Psoriasis and Psoriatic Arthritis Alliance	There doesn't appear to be any discrimination issues that have not been considered.	Comment noted. No action required.
The Psoriasis Association	Patients are frequently expected to, and often desire to self-care. This treatment provides the patient with this option. Patients are entitled to have a choice of treatment at the right time, and the best treatment. Golimumab provides a unique dosing regimen providing patients and clinicians with a treatment option that least impacts on daily living and quality of life. Unfortunately there is not one treatment that is successful for all people with Psoriatic Arthritis; therefore patients should be able to access all suitable treatments. Etanercept was used as the comparator, however we heard from the expert witnesses, and can see from the research evidence presented that etanercept does not work for all patients. Indeed patients have benefited by switching to another anti-TNF therapy. The Psoriasis Association therefore feels that golimumab should be recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met (as per TA199). • The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and • The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination	The Committee understood that people may prefer the option of a treatment that is self-injectable and/or has a longer retreatment interval (see FAD section 4.2) The Committee considered the evidence of comparative clinical effectiveness in light of comments received on the ACD. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). As no evidence was provided by the manufacturer regarding the use of golimumab after the failure of other TNF inhibitors, the Committee was unable to any recommendations for golimumab after the use of other TNF inhibitors (see FAD section 4.15). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Pathologists	The Royal College of Pathologists understands that NICE has not recommended golimumab or the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.	Comment noted. No action required.
Royal College of Pathologists	NICE has recommended adalimumab, etanercept and infliximab for the treatment of psoriatic arthritis when the psoriatic arthritis has not responded to adequate trials of at least two standard DMARDs. Although all anti TNF drugs act on TNF cytokine pathway, the exact mechanisms of the actions of various anti TNF agents are not identical hence, not recommending golimumab from the armoury for the treatment of psoriatic arthritis, reduces the chance of identifying a subgroup of patients who might benefit from this.	The Committee considered the extent to which the TNF inhibitors could be considered equally effective. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
Royal College of Pathologists	It is known that the route and frequency of golimumab administration is beneficial for some patients compared to some other anti TNF agents. This disadvantages some patients who are significantly disabled from the disease, if Golimumab is not recommended.	The Committee understood that people may prefer the option of a treatment that is self-injectable and/or has a longer retreatment interval (see FAD section 4.2). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Nominating organisation	Comment	Response
Royal College of Pathologists	In the first instance, the Royal College of Pathologists would request NICE to recommend golimumab in patients with psoriatic arthritis who have not responded to DMARD and two anti-TNF agents.	The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
Royal College of Pathologists	NICE should recommend further head to head trials with established anti TNF agents with golimumab and maintain a register for adverse reactions.	The Committee noted the importance of registries in gathering data and supported the inclusion of outcomes specific to psoriatic arthritis in a suitable registry (see FAD section 4.18).
Royal College of Nursing	The evidence considered seems comprehensive.	Comment noted. No action required.
Royal College of Nursing	We would ask that the summaries of the clinical and cost effectiveness of this appraisal be aligned to the clinical pathway followed by patients with psoriatic arthritis. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	The Committee considered the current clinical practice for the treatment of psoriatic arthritis (see FAD section 4.3). The Committee does not base its decision on the potential budget impact of a technology. The Committee takes account of how its advice may enable the more efficient use of available healthcare resources, as represented by estimates of incremental cost effectiveness (see Guide to the Methods of Technology Appraisal, section 6.2.14).
Royal College of Nursing	Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and have no further comments to add to the document.	Comment noted. No action required.
Royal College of Nursing	We are not aware of any specific equality issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. Guidance on the use of this technology should also be mindful of the impact it may have on reducing socio-economic inequalities.	Comment noted. The Committee considered that its recommendations doenot differently impact on any group currently protected by the equalities legislation.

Nominating organisation	Comment	Response
British Health Professionals in Rheumatology	BHPR noted the comment in 4.4 – possibility of longer retreatment interval resulting in longer periods of discomfort due to 12 day half life – is there any evidence for this statement as we were unable to find any? This is particularly important as patients generally prefer a less frequent dosing schedule as it enables them to continue working and maintain their financial independence.	The Committee understood that people may prefer the option of a treatment that is self-injectable and/or has a longer retreatment interval (see FAD section 4.2). The Committee noted that the longer retreatment interval associated with golimumab could potentially result in more discomfort because of waning efficacy before retreatment. It concluded that golimumab could, on balance, be a valued additional treatment option for people with psoriatic arthritis (see FAD section 4.4).
British Health Professionals in Rheumatology	BHPR noted the comment in 4.6 – use of 100mg dose. The dose at 100mg would not be used within clinical practice and therefore this dose should not be included in the TA.	The 100mg dose is included in the marketing authorisation for golimumab (see FAD section 2.3). The Committee heard from the clinical specialists that they would probably use to a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6).
British Health Professionals in Rheumatology	Comment 4.8 – adverse events. The evidence suggests that there is no difference in the side effect profile of Golimumab compared to other TNF's and this has already been addressed by the licensing authority.	Following consultation on the Appraisal Consultation Document, the Committee considered additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis. It concluded that although there remains uncertainty about golimumab's long-term adverse event profile, it had not been shown to be different from that of other TNF inhibitors (see FAD sections 3.8 and 4.10).

Nominating organisation	Comment	Response
NHS Cambridgeshire acting on behalf of NHS Havering	The evidence on the impact of activity (e.g. day case) activity on the relative costs of the drugs does not appear to have been fully taken into account. Evidence on relative cost of administering each product is included in the ACD. However, I can confirm that current activity cost from a selection of providers shows an average cost of £740 i.e. a cost to administer the alternative infliximab that is three times the figure quoted cost from NICE of administering infliximab in other TAs. NICE is asked to review its evidence on the cost of administration of alternative products when considering the relative cost effectiveness of these agents	Comment noted. The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 (see FAD sections 1.1 and 1.2). The specifications for use in TA 199 require treatment to be initiated with the least expensive drug, taking account of drug administration costs, required dose and product price per dose.
NHS Cambridgeshire acting on behalf of NHS Havering	SIGN guidance on management of Psoriasis and Psoriatic Arthritis is due to be published in November 2010. Whilst that is Scottish guidance, and NICE relates to England and Wales, the Appraisal Committee is requested to take account of that information as that potentially relevant evidence on clinical opinion was brought to the Committee's attention through a clinical expert's submission. Failure to cross reference to such evidence as that from SIGN guidelines creates confusion and can make it harder for consultants and commissioners to implement NICE guidance consistently.	NICE has developed tools to help organisations put this guidance into practice. These are available on the website, the link to which is provided in the FAD (see section 5.2).
NHS Cambridgeshire acting on behalf of NHS Havering	From a commissioning perspective the ACD says too little to link this guidance to that published recently by NICE on the use of other antiTNFs in this disease. Therefore absence of clear cross reference to the implications of the other NICE guidance leads many to read the ACD in isolation, even though the relevant NICE documents are quoted near the end of the ACD.	The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199, which is the other piece of NICE guidance on the treatment of psoriatic arthritis (see FAD sections 1.1 and 1.2). TA 199 is cross-referenced throughout the FAD, and a hyper link is included in section 1.

Nominating organisation	Comment	Response
NHS Cambridgeshire acting on behalf of NHS Havering	The demonstrated difference in effectiveness as well as cost effectiveness of the different antiTNFs used in the evidence considered are reasonable, but when reported the impact of these differences on benefit for patients is difficult understand; the interpretations are not worded sufficiently clearly to be a useful guide for patients, consultants or commissioners.	For consultants and commissioners, NICE has developed tools to help organisations put this guidance into practice. These include costing templates, audit support and commissioning guides. These are available on the website, the link to which is provided in the FAD (see section 5.2). For patients, their families or carers, or for anyone with an interest the conditions for which guidance has been produce, NICE also publishes 'Understanding NICE Guidance', which offers a plain English summary of the recommendations included in a technology appraisal. These can be similarly found on the website.

Nominating organisation	Comment	Response
NHS Cambridgeshire acting on behalf of NHS Havering	**Are the provisional recommendations sound and a reasonable basis for guidance to the NHS?** Not entirely. Issues of relative benefit and potential problems, against other options, should more clearly be set out. If that is not properly addressed a drop in price through a patient access scheme will cloud the awareness of professionals and patients about the potential disbenefits for some including (a) longer periods when there may be reduced symptom relief, (b) lower efficacy, (c) latex in the product	Comment noted. Section 2.2 of the FAD provides an overview of the contraindications and the adverse reactions of golimumab, including reference to the potential allergic reactions in people with latex sensitivity. For full details of adverse effects, contraindications, special warnings and precautions for use, see the SPC. The Committee considered the extent to which the TNF inhibitors could be considered equally effective. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee concluded that although there remains uncertainty about golimumab's long-term adverse event profile, it had not been shown to be different from that of other TNF inhibitors (see FAD section 4.10).
NHS Cambridgeshire acting on behalf of NHS Havering	Section 2.2 of the ACD refers to situations in which golimumab either should not be used or where caution is required. NICE is asked to add to this section of the appraisal the fact that latex is present in the golimumab syringe (confirmed by the manufacturer at the Appraisal Committee hearing). This could cause a life-threatening reaction in some patient or their families or carers and they would be disadvantaged if this were not highlighted.	Section 2.2 of the FAD includes a reference to the potential allergic reactions in people with latex sensitivity.

Nominating organisation	Comment	Response
British Association of Dermatologists	The Therapy & Guidelines and the Biologics Register Sub-committees of the British Association of Dermatologists have reviewed this draft ACD on the use of golimumab for the treatment of psoriatic arthritis. All of the relevant evidence appears to have been taken into account, and the summaries of the clinical and cost effectiveness of golimumab represent reasonable interpretation of the evidence. The provisional recommendations form an appropriate basis for guidance as to the use of golimumab in the NHS, and contain no discriminatory aspects. There were no comments relating to the evaluation report, and no specific comments relating to the efficacy of golimumab in the treatment of the cutaneous manifestations of psoriasis.	Comment noted. No action required.
MSD (formerly Schering-Plough Limited)	Schering-Plough Limited, which is now part of MSD (MSD), welcomes the opportunity to comment on the ACD, which sets out the Appraisal Committee's (the Committee) recommendations on golimumab for the treatment of psoriatic arthritis (PsA).	Comment noted. No action required.
MSD (formerly Schering-Plough Limited)	We are disappointed that the Committee, having reviewed all of the evidence as well as hearing from stakeholders, has not felt able to recommend golimumab for the treatment of patients suffering from PsA.	Golimumab is now recommended for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
MSD (formerly Schering-Plough Limited)	MSD believes that there is a role for golimumab, based on significantly reduced injection frequency and lower injection site reactions, reducing pain and discomfort for the patient leading to a better quality of life. In addition, it provides physicians with a further treatment option to enable the more effective management of PsA. This was clearly articulated by the patient representatives and the clinical experts in both submissions to, and depositions at the Committee meeting.	The Committee understood that people may prefer the option of a treatment that is self-injectable and/or has a longer retreatment interval (see FAD section 4.2).

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	In the light of the wording of the ACD as well as the discussions that took place during the open session of the Committee meeting, MSD believes that the Committee's recommendation was influenced by the unbalanced presentation of the evidence to them.	The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of golimumab, having considered evidence on the nature of psoriatic arthritis and the value placed on the benefits of golimumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources and the impact of the patient access scheme.
MSD (formerly Schering-Plough Limited)	**General Observations** MSD considers that the ACD is misguided in the following respects: • The Committee's apparent use of a single efficacy criterion to decide on the relative clinical efficacy of golimumab compared with infliximab, adalimumab and etanercept; compounded by inappropriate use and interpretation of the outputs from various mixed treatment comparisons. • The undue weight given by the Committee to using safety as a decision criterion. MSD takes the view that the relative weighting attached to each of these by the Committee, further details of which are set out below, in arriving at the provisional recommendation under discussion lays the recommendation open to challenge from a process perspective.	The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdHS score from baseline (see FAD sections 4.8 & 4.9). The Committee understood the adverse effects of each of the technologies. It concluded that although there remains uncertainty about golimumab's long-term adverse event profile, it had not been shown to be different from that of other TNF inhibitors (see FAD section 4.10).
MSD (formerly Schering-Plough Limited)	**A. Reliance on one treatment efficacy measurement as assessed within the Mixed Treatment Comparisons methodology to inform decision making around comparative efficacy** **1. Single treatment efficacy criterion** Patients with a diagnosis of PsA are a heterogeneous group and in response to this a number of instruments have been developed to evaluate the efficacy of management strategies, including pharmacological treatments. For example, the GO-REVEAL study (Kavanaugh, et al, 2009) measured the following:	The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdHS score from baseline (see FAD sections 4.8 & 4.9). Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity, on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD

Nominating organisation	Comment	Response
	• Psoriatic Arthritis Response Criteria (PsARC) • Psoriasis Area and Severity Index (PASI) • American College of Rheumatology 20% improvement criteria (ACR20) • American College of Rheumatology 50% improvement criteria (ACR50) • American College of Rheumatology 70% improvement criteria (ACR70) • Health Assessment Questionnaire (HAQ) • Nail Psoriasis Severity Index (NAPSI) • EULAR response • Disease Activity Score (DAS28-CRP) • Enthesitis assessment • Morning stiffness assessment • Dactylitis assessment It appears that the Committee has focussed primarily on only one efficacy measure, the HAQ, which is a self-reporting assessment of functional ability, when deciding on the clinical efficacy of golimumab. This approach is not consistent with current clinical practice or previous NICE guidance in this area, where the measurement of effectiveness is assessed by reference to joint response; PsARC, or the American College of Rheumatology improvement criteria (ACR), plus the use of PASI to assess skin response. In addition, the recently published guidance TA199 -Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, support this approach: *"The Committee considered the clinical-effectiveness data presented by the manufacturers and noted that etanercept, infliximab and adalimumab all showed a statistically significant response in the joint disease (PsARC, ACR) and skin disease (PASI) criteria at 12-week and 24-week follow-up compared with placebo"*	section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Nominating organisation	Comment	Response
	"….. Although the indirect comparison conducted by the Assessment Group suggested that infliximab is the most effective treatment overall, taking into account both skin and joint disease, the Committee concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of individual TNF inhibitors in the treatment of psoriatic arthritis." The British Society of Rheumatology (BSR) Guidelines for the use of TNF Inhibitors in patients with PsA recommends an assessment of PsARC and PASI together to assess response to treatment Where alternatives are chosen, the decision is still based on use of an instrument that examines response across a range of measures. For example, this approach was followed in a recent analysis from the BSR by using the European League Against Rheumatism (EULAR)	
MSD (formerly Schering-Plough Limited)	**2. Mixed Treatment Comparisons** The use of the HAQ score in (virtual) isolation is compounded by the effect of the methodology used to compare golimumab with etanercept, adalumimab and infliximab, namely, Mixed Treatment Comparisons (MTC). MTCs potentially have a role in guiding an understanding of whether a range of technologies may be comparable in the absence of head to head data. Caution should however be exercised when using the findings from such a methodological approach to support ranking decisions within a class/group of technologies. The 2008 Methods Guide to Process references the use of indirect comparisons and mixed treatment comparisons but fails to clarify the uncertainty associated with the use of such methodologies. As such caution should be used when considering how to reflect any findings in Committee decisions. In the last three years, the NICE Executive has apparently moved from a position of accepting that MTC methodologies *may* provide supporting evidence to inform the decision of a Committee faced with uncertainty, to one of accepting that a Committee can use the results from such an analysis to *reliably* make ranking decisions within a class of technologies. Whilst MSD supports the development of alternative methodologies to inform decision making by payers it does not believe that MTCs can ever be used as a credible alternative to 'head to head' &/or placebo controlled RCTs, to safely	The HAQ score, nor the results of the MTC, were considered in isolation. The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdHS score from baseline. The Committee was also aware of the limitation of mixed treatment comparison methodology (see FAD sections 4.8 & 4.9). The Committee has now recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Nominating organisation	Comment	Response
	support clinical decision making that involves choice within a class of drugs. Methodological experts, experienced in clinical data analysis, have expressed concerns regarding the robustness of the MTC methodology over and above the information provided from primary RCTs. The Cochrane collaboration arguably comprises the grouping of people most interested in, and knowledgeable about, synthesis of clinical data to aid clinical decision making. MTCs are an ongoing point of interest with a number of experts experienced with MTC methodology and they have consistently indentified that caution needs to be used when attempting to apply findings to clinical decision-making compared with use of results from original RCTs. A recent analysis to establish whether MTCs can ever provide a robust platform for clinical or payer decision making has provided evidence that all such analyses are likely to be underpowered in relation to being able to support ranking decisions about a group of technologies	
MSD (formerly Schering-Plough Limited)	In the light of the above, we feel that the Committee should take the following into account in its further deliberations: **<u>1. NICE remit</u>** MSD is concerned that NICE, through the actions of the Committee, is acting at odds with the NICE Guide to the Single Technology Appraisal (STA) process.[1] This includes the following definition of the Medicines and Healthcare Products Regulatory Agency (MHRA) *"The Executive Agency of the Department of Health. It protects and promotes public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely".* That NICE acknowledges the role of the MHRA in ensuring the safety of medicines in the UK reflects our understanding of the difference between the	Following consultation on the Appraisal Consultation Document, the Committee considered additional evidence regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD sections 3.8 and 4.10). NICE only issues guidance in accordance with a technologies marketing authorisation.

[1] http://www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf

Nominating organisation	Comment	Response
	two agencies. We note that the role of NICE as set out in the Directions from the Secretary of State[2] does not define, for medicines, any role regarding evaluating safety and by extension does not require NICE to consider long term safety data (other than in relation to comparators around relative adverse event rates) in the Committee's decision-making process.	
MSD (formerly Schering-Plough Limited)	**2. Guidance issued by NICE regarding TNF Inhibitors as a class** MSD recognises that each of the four NICE guidance Committees is independent and also could, in principle, produce a different set of recommendations from other Committees, having deliberated upon the same evidence base. Despite this, MSD understands that the NICE Executive has a role in providing advice to its Committees based on previously generated and related NICE guidance so as to achieve coherence and consistency. This is done, if not for the sake of the patients and clinicians affected by NICE guidance, to allay potential concerns regarding the robustness of the process underpinning NICE guidance and to reduce the potential grounds for appeal. Regarding consistency of recommendations, previous Committees have reflected on the long term safety of TNF inhibitors. They have concluded that for a new technology which does not possess long term efficacy and safety data, the consideration of the importance of this should be left jointly to the patient and clinician as one of a number of factors that are considered in reaching treatment decisions. An exhaustive review of comments from NICE guidance regarding the safety of TNF Inhibitors provides the following support: a) TA180. Ustekinumab for the treatment of adults with moderate to severe psoriasis. *"The Committee heard from the clinical specialists that ustekinumab is a new drug that has been given to far fewer people than the other biological therapies, and therefore its long-term safety profile is less certain. Because of this, the specialists considered that the drug may initially be prescribed more cautiously than existing treatments. The Committee also heard from the clinical specialists and patient experts that people with severe psoriasis are often well informed about drug safety and able to consider benefits and risks before starting treatment (section 4.4. p.16)".*	The Committee considered the extent to which the TNF inhibitors could be considered equally effective. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has now recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

[2] http://www.nice.org.uk/niceMedia/pdf/DirectionFromSecretaryOfState2005.pdf

Nominating organisation	Comment	Response
	No mention is made in this guidance of the stated uncertainty driving any concerns re: comparative cost-effectiveness. b) TA186. Certolizumab pegol for the treatment of rheumatoid arthritis. No mention of safety either in principle or in relation to any long-term uncertainty regarding cost-effectiveness. c) TA187. Infliximab (review) and adalimumab for the treatment of Crohn's disease. The following mention is made of safety re: infliximab and adalimumab: *"The Committee heard from the clinical specialists that they were concerned about the longer-term effectiveness and safety of infliximab and adalimumab".* This did not translate into a decision by the Committee to restrict access, or to any (expressed) long-term uncertainty regarding comparative cost-effectiveness. It should be noted that this concern about longer-term (effectiveness and) safety relates to two technologies which had been in use in the UK for a number of years; the conclusion being that expert clinicians would only be confident about the longer term safety of *any* of the TNF inhibitors, after a significant number of patients had received one or other of the TNF inhibitors over a number of years far in excess of any of the available currently licensed TNF inhibitors. d) TA198. Tocilizumab for the treatment of rheumatoid arthritis A discussion describes comparable AE rates with other TNF Inhibitors and the following statement appears: *"Approximately 14% of people discontinued tocilizumab treatment for safety reasons (including intercurrent illness)".* e) TA199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Given that this Technology Appraisal (TA) is a recently updated Multi Technology Appraisal (MTA) (published August 2010) providing guidance for the three comparative therapies included in the golimumab appraisal (infliximab, adalumimab, etanercept) and for the same disease, it is arguably not only the most relevant, but also likely to be the most helpful in guiding related decision-making.	

Nominating organisation	Comment	Response
	In TA199, when referring to adverse events rates for each technology, the following comment is made for each one when it is described in the guidance: *"For full details of undesirable effects and contraindications, see the summary of product characteristics."* The guidance goes on to state: *"Overall, the limited evidence prevented them from drawing firm conclusions from the systematic review about the comparative adverse event profile of the three TNF inhibitors".* The statements above are supported by two systematic reviews and a recent review of data regarding patients with a diagnosis of PsA within the British Society of Rheumatology Biologics Registry (BSRBR).	
MSD (formerly Schering-Plough Limited)	**3. STA process** The scope for the appraisal of golimumab in patients with psoriatic arthritis is stated as follows: *"To appraise the clinical and cost-effectiveness of golimumab, within its licensed indication, for the treatment of psoriatic arthritis."* Safety is not included in the remit, although within the scoping document one of the outcomes stated to be measured is 'adverse events'. As a stakeholder, MSD understands that the measurement of adverse events is a necessary component for a comprehensive cost utility analysis, where the cost of treating such events could influence the final Incremental Cost Effectiveness Ratio (ICER). MSD also understands that this is divorced from the Committee making decisions about whether a product should be approved or not based on the presence/absence of long-term safety data.	Following consultation on the Appraisal Consultation Document, the Committee considered additional evidence regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD sections 3.8 and 4.10). NICE only issues guidance in accordance with a technologies marketing authorisation.

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	**Clinical efficacy of golimumab in relation to etanercept, infliximab and adalumimab** MSD believes that a key determinant of the recommendation within the ACD is driven by the belief that etanercept is clinically superior to golimumab. The weight that must have attached to this within the decision-making of the Committee is provided by a comment from the Evidence Review Group (ERG) report: *"However, a key area in determining the cost-effectiveness of anti-TNF agents is whether they should be considered equally clinically effective, that is, to treat them as a class. This was the position adopted in the guidance issued by NICE following the previous appraisal of etanercept, adalimumab and infliximab for psoriatic arthritis. If all anti-TNF agents are considered equally effective (in terms of PsARC, HAQ[3] and PASI responses) then etanercept, adalimumab and golimumab have very nearly equal costs and equal QALYs and all have an ICER of about £15,000 per QALY versus palliative care [ERG report – section 1.5]".* The issues around this apparently breakdown into: 1. Focus on a single measure of effectiveness; the HAQ score. 2. Reliance on MTC results to inform the Committee decision.	The Committee considered the extent to which the TNF inhibitors could be considered equally effective. The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdHS score from baseline. The Committee was also aware of the limitation of mixed treatment comparison methodology (see FAD sections 4.8 & 4.9). Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity, on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has now recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

[3] HAQ was not one of the key determinants of relative efficacy used in TA.199; the three cited are PsARC, ACR and PASI.

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	**1. Focus on a single measure of effectiveness** In the above quote from the ERG report, we note that they have included HAQ as one of the three response criteria. This stands apart from; TA199 guidance which discusses response in relation to PsARC, ACR and PASI, whilst BSR guidelines mention two (PsARC and PASI). Neither TA199 nor the BSR Guidance suggest that HAQ is a key criterion for assessing clinical efficacy of TNF Inhibitors. This ERG highlighting of HAQ as one of the response criteria, is reflected throughout their report. It was also highlighted in the clinical presentation to the Committee, and is reflected in the ACD itself. This is also consistent with the York approach to TA199 although notably this was not reflected in the TA199 Committee deliberations or decision-making. The Committee has primarily focussed on just one efficacy measure, HAQ, when deciding on the relative clinical efficacy of golimumab. This does not conform either to current clinical practice or previous NICE guidance in this area, and may have been driven by the approach of the ERG to evidence analysis and its subsequent presentation.	The Committee did not base its decision on a single efficacy criterion. The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdHS score from baseline (see FAD sections 4.8 and 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
MSD (formerly Schering-Plough Limited)	**2. Reliance on MTC results to inform the Committee decision** The NICE methods guide makes the following statement; *When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework* ***if it is considered to add information that is not available from the head-to-head comparison (emphasis added).*** MSD believes that the MTC does not add to the understanding of golimumab in relation to infliximab, adalumimab and etanercept. The principal rationale for the MTC approach within Health Technology Appraisal, over and above an adjusted indirect comparison approach, lies where there is a mix of data ('head to head' studies and placebo controlled studies). In the analysis under consideration all data is from placebo controlled studies each of a single TNF Inhibitor.	The Committee has now recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2). The results of the MTC were not considered in isolation. The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdH-S score from baseline. The Committee was also aware of the limitation of mixed treatment comparison methodology (see FAD sections 4.8 & 4.9). Although the evidence suggested that golimumab

Nominating organisation	Comment	Response
	The Committee's view that etanercept is clinically superior to golimumab is based on an analysis of three MTCs, namely, MSD's MTC for their submission (MS MTC), MSD's adapted MTC with inputs requested by the ERG (MS/ERG MTC)[4], and an MTC developed by the ERG (York MTC). The ERG, and subsequently the Committee, concentrated on the comparative analysis of HAQ scores within the MTCs. MSD does not agree with this approach. MSD believes that HAQ scores have been promoted and used because they drive the potential for differentiating the technologies on cost-effectiveness grounds and therefore support an incremental ranking of the four TNF inhibitors in terms of dominance and extended dominance. MSD's key concern around the applicability of these MTC analyses lies in the heterogeneity between the original RCTs included in the analysis with all three MTCs (reliant on the same 7 RCTs) generating different findings for a number of outcomes, especially HAQ scores. In relation to HAQ, a comment within the ERG report states: *"Despite some differences in the mean HAQ score at baseline between the included trials, there was a high variability of these HAQ values (high standard deviation) and, thus, it is very likely that differences in mean HAQ scores were not significant. Although there was a concern about the correlation between baseline HAQ scores and absolute HAQ changes in these PsA patients, given such a high variability of these HAQ values,* ***the ERG considered the exchangeability of mean HAQ scores across the included trials in the MTC analysis to be acceptable." (emphasis added)*** MSD does not believe that ERG's approach above should be adopted. The ERG's approach has a significant impact on the comparative analysis given the width of the CrIs and the overlap with placebo, with a particular concern about the role of one of the etanercept studies .[5] As a result of the more standardised and/or broader nature of the instruments, the PsARC and PASI results are more in line with the underpinning RCTs and the clinical understanding of the relative efficacy of the four technologies.	may be less effective in its anti-arthritic activity, on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9).

[4] MS/ERG MTC was adapted at the request of the ERG not because of errors but rather to conform to the York understanding of TA199

[5] (Mease et al, 2000).

Nominating organisation	Comment	Response
	In relation to the use of MTCs for golimumab, the GO-REVEAL study provided HAQ data for the analysis. Absolute changes in HAQ score were subsequently available to both MSD and the ERG. In contrast to this, MSD was forced to use the York analysis[6] as the data source for the etanercept trials given the absence of (appropriately presented) HAQ data from the published study reports. The York analysis builds on Commercial In Confidence (CIC) data on HAQ change with etanercept that are not publicly available (or, in the case of Mease 2000, not available for the groups of responders and non-responders separately). MSD believes that the Mease 2000 data should have been removed from the MTC because: 1. It reported an average change in HAQ using aggregated HAQ changes of -0.1 with placebo or -1.2 with etanercept, i.e. a difference to placebo of -1.1. In the results of the MS/ERG MTC, the average HAQ change associated with etanercept (averaged across the response groups) is estimated as -0.57, the difference to placebo is -0.52. This is a composite estimate of Mease 2000 and Mease 2004 and within the framework of the MTC. MSD cannot be precise about the values that went into the York meta-analysis without access to the CIC etanercept data, but if the mean difference in the York analysis is -0.52 and in Mease 2000 is -1.2, then in Mease 2004 it must be smaller in magnitude than the composite mean (possibly -0.4 or -0.3 or so, depending on the size of the studies and variation between patients). *The corresponding value for those patients in receipt of golimumab 50mg from the GO-REVEAL study was -0.33. 2. 34% of etanercept-treated patients achieved a HAQ score of '0'. This dramatic improvement has not been replicated in either Mease 2004 or the etanercept RA studies. We understand that the smaller study Mease 2000 (sixty patients, single centre and also reported in 2000) is adding significantly to the improvement in HAQ changes seen with etanercept. It would be appropriate, given the discrepancies noted above, to conduct an analysis excluding Mease 2000.	The Committee had misgivings about the selective removal of individual trials, but heard from the ERG that extracting the Mease 2000 study from the mixed treatment comparison had little effect on the results (see FAD section 4.7)

[6] Woolacott et al, 2006

Nominating organisation	Comment	Response
	MSD believes that this analysis would be more relevant for understanding the comparative HAQ values given, not only the markedly differing HAQ values above, but also the other differences illustrated in Table 1. [Table 1: Selected Mease 2000, Mease 2004 and GO-REVEAL study characteristics included in comment, but not reproduced here.]	

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	For HAQ, the lower bounds of the 95% CrIs for golimumab and infliximab overlap the upper bound of the 95% CrI for placebo. This raises further questions regarding the applicability of the findings from the MTCs as trial results were each statistically significant and infliximab was suggested as being the more efficacious of infliximab, etanercept and adalumimab in TA199. With the combination of significant uncertainty re: the validity of some of the HAQ data plus the evidence for significant heterogeneity between Mease2004 and Mease2000, MSD does not believe that the HAQ data as currently described can be used to help inform any comparative analysis, whether in isolation or as part of a composite. An examination of the differences between three data analyses, HAQ from the MS/ERG MTC (Figure 1) PsARC from the MS/ERG MTC (Figure 2) and PASI from MS/ERG MTC (Figure 3) demonstrates the challenges of arriving at meaningful conclusions because of inconsistent of results across instruments and issues concerning heterogeneity from the core data. [Figure 1: HAQ responders – MS/ERG MTC; Figure 2: PsARC responders – MS/ERG MTC; Figure 3: PASI responders – MS/ERG MTC included in comment, but not reproduced here.] The PASI responders (Figure.3) and PsARC responders (Figure.2) analyses point estimates and CrIs conform to the clinician understanding of drugs in this class and validate the conclusions reached in TA.199 regarding comparative clinical efficacy. This data demonstrates the importance of evaluating effectiveness of a drug by multiple parameters instead of only one.	The results of the MTC were not considered in isolation. The Committee considered the relative efficacy of the technologies in terms of PsARC response, PASI change from baseline, change in HAQ score and change in vdH-S score from baseline. The Committee was also aware of the limitation of mixed treatment comparison methodology (see FAD sections 4.8 & 4.9). Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity, on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9).

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	**Absence of long-term safety data** The Committee has placed significant emphasis on safety in arriving at its preliminary recommendation The Committee devoted the majority of the open session of their meeting to discussing the safety of golimumab and particularly events that occurred in the GO-REVEAL trial, even although it was accepted that this trial, GO-REVEAL, was not powered to examine safety. There was also discussion around the significance of the half life of golimumab in relation to concerns about, and management of, intercurrent infections. <u>Golimumab half life</u> *"The half life of Simponi (golimumab) is 12 +/- 3 days" which is similar to that of adalimumab (SPC states approximately two weeks), infliximab (SPC states 7.7-9.5 days) and etanercept (SPC states approximately 4.3 days Of note, in the Phase 3 PsA study with SC golimumab through Week 104, the incidence of serious infections per 100 subject-years follow up was 9.41 (CI: 2.56, 24.08) in the placebo group (subjects treated with placebo at Week 0 through a change in treatment to golimumab or the last safety visit), 0.84 (CI: 0.17, 2.45) in the golimumab 50 mg group, and 1.20 (CI: 0.33, 3.07) in the golimumab 100 mg group with the 95% CI's for the golimumab groups excluded from or overlapping the placebo group. These rates are similar to those reported in the Humira (2.4 per 100 subject-years[7]"* Regarding intercurrent infections, physicians who prescribe TNF Inhibitors are both familiar with the risks and are also best placed to manage intercurrent infections.	NICE only issues guidance in accordance with a technologies marketing authorisation. Following consultation on the Appraisal Consultation Document, the Committee considered this additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD section 3.8). It concluded that while there remains uncertainty about golimumab's long term adverse event profile, it had not been shown to be different from that of the other TNF inhibitors (see FAD section 4.10). The Committee noted that the longer retreatment interval associated with golimumab could potentially result in more discomfort because of waning efficacy before retreatment. It concluded that golimumab could, on balance, be a valued additional treatment option for people with psoriatic arthritis (see FAD section 4.4).

[7] (Mease et al,2009).

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	[redacted]	Comments noted.

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	**Dose escalation of golimumab affecting its cost-effectiveness** It appears that the Committee has decided that dose escalation will occur to a degree significant enough to make golimumab not cost-effective for use in England and Wales, although the clinical opinion provided to the ERG and the Committee differs. It remains our position that dose escalation from 50mg to 100mg will not occur except in rare instances.	The Committee heard from the clinical specialists that they would be more likely to use a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6).
MSD (formerly Schering-Plough Limited)	1. Dose escalation per label is only allowed for subjects greater than 100kg and is unlikely given UK clinical practice. This is based upon the SmPC. The part of the SmPC in section 4.2 that discusses dose escalation does not refer to dose escalation in the general PsA patient population; rather it states that for patients weighing greater than 100 kg who have not achieved a clinical response after 3 or 4 doses, increasing the dose of golimumab to 100mg once a month may be considered. Additionally, continued therapy is recommended to be reconsidered for those patients who do not show improvement after 3-4 doses of 100mg. *"In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in* patients *who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg."* MSD is aligned with clinical experts familiar with UK clinical practice in believing that dose escalation for patients who weigh less than 100kg will not occur and is not per SmPC guidance. For the small group of patients who weigh more than 100kg (7% of the BSR registry) the SmPC does not *recommend* dose escalation in those patients who have an inadequate response; rather it states that it *may* be considered: *In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after*	The Committee was aware of the label specifications for the use of the 100mg dose. The Committee heard two varying opinions on the proportion of people who would be eligible for the 100mg dose, and agreed that this portion was uncertain (see FAD section 4.14). The Committee heard from the clinical specialists that they would be more likely to use a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6).

Nominating organisation	Comment	Response
	receiving 3 to 4 additional doses of 100 mg…..' The EMEA rationale for including this in the SmPC is that patients who weighed >100kg treated with golimumab 100mg from the outset fared better than those treated with 50mg from the outset. For the group of patients weighing >100kg treated initially with golimumab 50mg who were dose escalated to 100mg there was no evidence of increased efficacy. Our position is supported by the clinical experts at the Committee meeting (aligned with the feedback to the ERG from the clinician they consulted) who stated that irrespective of weight they were far more likely to switch their patient who wasn't responding to the initial TNF Inhibitor, to an alternative TNF Inhibiter or other biologic rather than dose escalate.	

Nominating organisation	Comment	Response
MSD (formerly Schering-Plough Limited)	2. Dose escalation in the study is not indicative of what occurs in clinical practice. Given that the Committee, after reflecting on all of the above, believes that dose escalation is a significant issue, MSD wishes to reiterate that the proportion of patients who were likely to be dose escalated to 100mg within the GO-REVEAL study is not an indication of the degree of dose escalation likely to occur in clinical practice. The reason for this is that the GO-REVEAL trial design resulted in the dose escalation rather than individual clinical decision-making. Within the GO-REVEAL study there was a mandatory 'early escape' where dose escalation occurred in a blinded fashion if patients had a <10% improvement from baseline for both swollen and tender joints (blinding maintained). In the golimumab 50mg arm 20% of patients still receiving study medication at this stage were dose escalated. This would not be repeated in clinical practice in England and Wales. There are several reasons for this: 1. A number of the patients dose escalated would be considered non-responders in clinical practice and therefore be discontinued treatment. 2. Stopping rules as currently used in the UK would mean that the patients who were 'partial responders at the 'early escape' time point in the clinical study would be continued on treatment for 6 months. There is good evidence from the other TNF Inhibitors that for some patients it can take this long see the full benefits of the treatment. 3. There are alternative treatment options for patients who fail, or do not respond adequately, to an initial treatment option and clinicians have expressed a preference for switching the treatment given the evidence that patients who do not respond (adequately) to one biologic technology often do to another. There was no option within the trial design to discontinue study medication with a view to treating the patient with an alternative TNF Inhibitor or other biologic.	The Committee heard from the clinical specialists that they would be more likely to use a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6).
MSD (formerly Schering-Plough Limited)	[redacted]	Comment noted.

Nominating organisation	Comment	Response
	[redacted]	

Nominating organisation	Comment	Response
	[redacted] It is possible that the Committee conclude in its final guidance that there is no compelling evidence to support dose escalation to a total of 100mg pcm and therefore does not recommend clinicians to do so from the perspective of cost-effectiveness. Given that there is no direct clinical data supporting dose escalation for patients weighing >100kg, MSD will not be advocating dose escalation and would thus not be marketing golimumab at odds with such a recommendation were it to be included in the final guidance.	
MSD (formerly Schering-Plough Limited)	**Conclusion** MSD believes that the Committee arrived at their preliminary recommendation based on a misinterpretation of the evidence. MSD is confident that if the Committee reviewed the evidence in light of the points made in this letter it would arrive at a different conclusion; one which would enhance the physicians armamentarium and also provide a valuable option for patients who need flexibility in their treatment regimen to maintain a reasonable quality of life. For this reason we would urge the Committee to reconsider its decision based on the evidence presented above. MSD will cooperate in the provision of any other information or analyses that the Committee might wish to review so as to enable such a re-evaluation. We are grateful for the opportunity to comment on the ACD and look forward to continued dialogue with NICE regarding the issues raised in this response. [Appendix and references included, but not reproduced here.]	Comments noted. The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Comments received from commentators

Commentator	Comment	Response
Abbott	**1. Do you consider that all of the relevant evidence has been taken into account?** 1.1 Modelling of results to include patients requiring the 100mg golimumab dose The marketing authorisation for golimumab states that, "in patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered." However, no modelling was undertaken that included a proportion of patients weighing more than 100kg requiring the 100mg dose. This was the case even following a request from the ERG to provide a sensitivity analysis with the relevant proportion of the cohort on this higher dose with corresponding costs. Given that the higher dose is double the cost of the 50mg dose, Abbott considers that there should be some explicit wording around the use of the 100mg dose, particularly if the preliminary recommendations in the ACD change. In a European study evaluating the real world use of adalimumab in psoriatic arthritis patients (STEREO), 17.27% of the 440 patients enrolled weighed 100kg or more. Therefore, Abbott suggests that additional modelling be undertaken to explore the cost-effectiveness of golimumab including a percentage of patients receiving the higher golimumab dose as per the ERG's request i.e. the annual drug acquisition cost of golimumab should be weighted to include a range of patients requiring the higher dose to see the impact this has on the ICERs vs. standard care and the other anti-TNFs.	The Committee was aware of the label specifications for the use of the 100mg dose. The Committee heard two varying opinions on the proportion of people who would be eligible for the 100mg dose, and agreed that this portion was uncertain (see FAD section 4.14). The Committee heard from the clinical specialists that they would be more likely to use to a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6).
Abbott	**2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** In section 3.11 of the ACD, the Committee noted that "Of the four TNF inhibitors, golimumab had the lowest HAQ score change from baseline, both in participants whose disease responded to treatment based on PsARC score and those whose disease did not respond." Furthermore, in section 4.7 of the ACD it states "The Committee inferred that, based on the changes in HAQ score, golimumab and etanercept could not be assumed to be of equal efficacy." Abbott contends that the smaller improvements in the HAQ score reported for golimumab are inextricably linked to its radiographic progression data. 2.1 <u>It has not been shown conclusively that golimumab inhibits structural joint damage</u> There were two co-primary endpoints hypothesised in the statistical analysis of the	The Committee considered the evidence of comparative clinical effectiveness in light of comments received on the ACD. The Committee heard that since the ACD meeting, the manufacturer had applied for an extension of the golimumab license to include, among others, the reduction and the maintenance of reduction of structural joint damage. The Committee considered the radiographic progression data (vdH-S score) together with the change in HAQ score to assess the effect of treatment with golimumab on disease progression. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity

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	golimumab PsA trial: 1) the percentage of ACR20 responders at week 14, and 2) the change from baseline in PsA modified van der Heijde-Sharp (vdH-S) score at Week 24. Interestingly, the results for the second co-primary endpoint were not published in the Arthritis & Rheumatism paper discussing the 24 week efficacy and safety results; and neither were they submitted to the EMEA in the application for marketing authorisation: "Data for the co-primary endpoint of change from baseline in PsA modified van der Heijde-Sharp (vdH-S) score at Week 24 were not provided in this application." (Page 40 of the Scientific discussion from the EPAR for Simponi)2. Following a request from the ERG, the manufacturer provided the 24 week joint damage data. Results showed that the baseline vdH-S score for the 50mg golimumab group improved by -0.16 compared to a 0.27 worsening in the placebo group (p=0.01); and there were no statistically significant differences in the vdH-S score between the golimumab 100mg arm and placebo at week 24. These data suggest that golimumab has minimal impact in preventing joint damage. These findings are not consistent with those observed for the other three anti-TNFs. The GO-REVEAL golimumab trial used the vdH-S score to evaluate radiographic changes in the joints, this was the same scoring tool used in the infliximab trials. At week 24 in IMPACT 2, the mean improvement in the total baseline vdH-S score from baseline in the infliximab 5mg/kg group was -0.7 compared to a worsening of 0.8 in the placebo group (p<0.001 for the comparison). The mean baseline vdH-S score was slightly worse in the infliximab trial (30.3 ± 61.4 for infliximab 5mg/kg vs. 23.85 ± 35.41 for golimumab 50mg), however the difference in improvement from baseline between the two anti-TNFs is still four-fold. Although the adalimumab and etanercept PsA trials used a different scoring tool to calculate radiographic changes in the joints, both anti-TNFs showed highly statistically significant differences in the modified total Sharp score at week 24 compared to placebo (p<0.001). The radiographic data from the phase III trials of adalimumab, etanercept and infliximab resulted in the inclusion of specific wording in the licence to reflect this benefit. For example in the therapeutic indication section of the adalimumab SmPC it states: "…Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function". There is no such wording in the golimumab SmPC as the manufacturer did not include the radiographic data for golimumab in its regulatory application.	(based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9).

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	Interestingly, the apparent inability of golimumab to prevent structural joint damage has also been observed in the rheumatoid arthritis data. In the marketing authorisations for adalimumab, etanercept and infliximab there is explicit wording highlighting that the rate of progression of joint damage as measured by X-ray is reduced, whereas there isn't such a claim in the golimumab RA licence. This is because results from the GO-FORWARD study evaluating golimumab in RA patients who have had an inadequate response to methotrexate showed that there was no significant reduction in disease progression in patients with established RA receiving 50mg golimumab. There was some discussion that the trial population in the GO-FORWARD study seemed to be at a lesser risk of radiographic progression as the baseline characteristics of these patients were less severe than have previously been reported for the other anti-TNF trials; however there was still no difference in the mean change from baseline in the vdH-S score between the 50mg golimumab + methotrexate group and the placebo + methotrexate group at 24 weeks, 0.55 and 0.6, respectively. In summary, although golimumab controls the signs and symptoms of PsA as measured by ACR and PASI with similar efficacy to adalimumab, etanercept and infliximab; it has not demonstrated that it inhibits structural joint damage in the same way the other anti-TNFs do. It can therefore not be considered to have the same efficacy as adalimumab, etanercept and infliximab. Consequently, all the long-term benefits relating to preventing joint damage, captured in the model by assuming zero HAQ progression, should not be assumed for golimumab as there is currently little evidence to support this.	
Abbott	2.2 <u>Possible rationale as to why golimumab has not been shown to prevent joint damage</u> The European Medicines Agency discussed the rationale for the chosen doses of golimumab in the phase III clinical trial programme, 50 mg and 100mg every 4th week. The Agency concluded that the rationale for the choice was "not fully obvious" (Page 63 of the EPAR). Abbott suggests that the interval between doses of golimumab is too great to maintain tight disease control. This is evidenced by data in the EPAR discussion on serum trough levels of golimumab (outlined below). As a consequence patients are not achieving adequate control of their underlying disease, which may explain the lack of data showing that golimumab inhibits radiographic progression in both PsA and RA. On page 19 of the EPAR it discusses the pharmacokinetic data for golimumab. In most golimumab studies, serum concentrations of golimumab were measured using the sandwich ECLIA assay. The lower limit of quantification (LLOQ) of this assay	See comment above.

Commentator	Comment	Response
	was 200 ng/ml with an MRD (minimum required dilution) of 10, however, the EPAR notes that this limit was not low enough to estimate trough concentrations in all subjects following the administration of 50 mg every 4 weeks (q4w). In other words, even with a very low level of quantification to detect serum concentrations of golimumab, following the administration of 40mg every 4 weeks it was still not possible to detect trough concentrations in some patients. Furthermore, the EPAR notes on page 20 that, “median serum trough concentrations obtained over longer time periods indicate a tendency toward a decrease over time [up to 52 weeks], which may be related to increased formation of antibodies toward golimumab and possibly an increased risk of inefficacy.” Interestingly, as the LLOQ of the detection assay was not low enough to estimate trough concentrations in all subjects the observed median values may also be upward biased (EPAR, page 20). This coupled with a tendency toward a decrease over time suggests that serum levels of golimumab are too low when it is administered once every 4 weeks. The posology for golimumab states that it should be given once monthly, and not once every 4 weeks. This is because although dosing was scheduled at 4-week intervals, a 3 to 7 day dose window was specified in the protocol allowing for 30 to 31 day intervals if necessary. Abbott could not determine how many subjects made use of the 3 to 7 day window, and therefore does not know how many patients received golimumab less frequently than once every four weeks. However, if in some subjects serum trough levels of golimumab were not detectable following the administration of 50 mg every 4 weeks, it is a concern that an increased interval between doses will have serious implications for disease control. If a more frequent dosing regimen was implemented for golimumab, it is possible that the underlying disease would be better controlled, which would be supported by evidence of inhibition of radiographic progression. However, such a dosing regimen would have a substantial effect on the cost-effectiveness estimates.	

Commentator	Comment	Response
Abbott	2.3 Correlation between joint damage measured by X-ray and HAQ The importance of inhibition of radiographic progression is becoming increasingly apparent across all of the rheumatological diseases, with studies in rheumatoid arthritis having demonstrated that inhibition of radiographic progression has a meaningful impact on patients' lives in terms of both HAQ scores and employment status. Using data from an RCT of etanercept + methotrexate in patients with rheumatoid arthritis, van der Heijde et al. found that after adjusting for age, sex and disease activity, HAQ scores were significantly determined by both the absolute level of joint damage and the radiographic progression. The authors concluded that patients with greater radiographic damage, and those with recent radiographic progression, have a higher degree of disability. In a similar vein, analysis of data from an RCT of adalimumab + methotrexate in patients with RA found that radiographic progression was significantly correlated with employment status, indicating that this measure of disease has a direct impact on the patient. Figure 2.3 from the van Vollenhoven study shows the relationship between increasing joint damage measured by the Sharp score and the percentage of decreasing odds of gaining/maintaining favourable employment. [Figure 2.3: Relationship between worsening joint damage and the odds of being in employment – figure not presented here]	See comment above.

Commentator	Comment	Response
Abbott	2.4 Confusion around the HAQ changes from baseline in manufacturer's submission at weeks 14 and 24 On page 69 of the manufacturer's submission (MS), the mean change in HAQ score from baseline was presented for weeks 14 and 24. Table 2.4 reproduces the numbers from the MS below: Time point — Golimumab 50mg — Placebo 14 weeks — 0.3 — 0.4 24 weeks — 0.3 — -0.03 Abbott is unclear as to how to interpret these numbers. Given that the HAQ score ranges from 0 to 3, where 0 is equal to no disability and 3 equates to severe disability, improvements in HAQ are usually presented in the negative. If we assume that this convention has been reversed and that there is a 0.3 improvement at week 14 in the golimumab arm as opposed to a worsening, it appears that patients receiving placebo had a better improvement in their HAQ score then those patients receiving golimumab. Since this time point is before the early escape option at week 16 this presumably includes all patients in the placebo arm, including non-responders. If the week 14 placebo HAQ change is correct, then patients worsen considerably in just 10 weeks for the week 24 mean HAQ change from baseline to be -0.03. Given that changes in HAQ are key in the economic modelling, these numbers should be checked and amended as necessary in any subsequent analyses.	Comment noted.

Commentator	Comment	Response
Abbott	2.5 Estimation of nurse time required to teach subcutaneous administration In the manufacturer's submission, the cost of an additional 4 hours of nurse time was added on top of the outpatient visit to train patients to self-administer an anti-TNF. This cost was applied to all the subcutaneous agents: adalimumab, etanercept and golimumab. Abbott contends that this is a gross overestimation of the time taken to train patients to self-administer. In NICE clinical guidelines and costing templates of subcutaneously administered agents, the cost of a one hour training session with a Band 6 nurse has been used routinely for the time taken to train patients to self-administer with an injectable pen. Furthermore, for patients receiving adalimumab nurse training to teach self-injection is provided free of charge as part of the home delivery package.	The Committee noted that TA 199 states that treatment choice among the TNF inhibitors etanercept, infliximab and abatacept should be based on cost (taking into account drug administration costs, required dose and product price per dose), with treatment initiated with the least expensive drug. The Committee concluded that golimumab would be considered an acceptable option for the treatment of psoriatic arthritis if used with same restrictions as included in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD section 4.14).
Abbott	**3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** There is no conclusive evidence to show that golimumab prevents the progressive joint damage associated with psoriatic arthritis. Evidence shows that there is a correlation between radiographic progression and functional disability, plus other hard outcomes such as employment status. Given that the other anti-TNFs for PsA have demonstrated an ability to prevent progressive joint damage and therefore long-term functional disability, Abbott can understand why the Committee has made its preliminary recommendations for golimumab.	The Committee considered the evidence of comparative clinical effectiveness in light of comments received on the ACD. The Committee heard that since the ACD meeting, the manufacturer had applied for an extension of the golimumab license to include, among others, the reduction and the maintenance of reduction of structural joint damage. Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity , on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

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Abbott	**4. Are there any equality related issues that may need special consideration?** None that Abbott is aware of.	Comment noted. No action required.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	2	The cost of golimumab depends on the dose. Dose escalation is a risk to commissioners. The cost of £9,294.96 per patient per year, which is similar to the annual costs of other TNF-a inhibitors, was modelled by the manufacturer, the recommended starting dose is 50mg given once a month, given subcutaneously. However the drug has marketing authorisation for an increased to 100mg a month in people weighing more than 100kg whose psoriatic arthritis shows inadequate response after three or four doses. People taking the 100mg dose would incur twice the annual cost and it is not clear now many would do so.	The Committee heard two varying opinions on the proportion of people who would be eligible for the 100mg dose, and agreed that this portion was uncertain (see FAD section 4.14). The Committee heard from the clinical specialists that they would be more likely to use a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6). TA 199 states that treatment choice among the TNF inhibitors etanercept, infliximab and abatacept should be based on cost (taking into account drug administration costs, required dose and product price per dose), with treatment initiated with the least expensive drug. The Committee concluded that golimumab would be considered an acceptable option for the treatment of psoriatic arthritis if used with same restrictions as included in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD section 4.14).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 1	3	This technology is not a cost effective use of NHS resources. Golimumab is not as effective as the key comparator, etanercept. Indirect comparisons reporting quality of life change in Health Assessment Questionnaire [HAQ] score suggest that health related quality of life improves further with etanercept. The long term adverse effects of golimumab have not been adequately studied. The GO-REVEAL study was not sufficiently powered to detect differences in adverse event outcomes. The manufacturer did not provide any long term safety data for golimumab, though some data is available from trials of the drug for other indications. In addition golimumab is not included in the current British Society of Rheumatology Biologic Registry and so there is no mechanism for monitoring the number of severe adverse events that might occur.	Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). Following consultation on the Appraisal Consultation Document, the Committee considered this additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD section 3.8). It concluded that while there remains uncertainty about golimumab's long term adverse event profile, it had not been shown to be different from that of the other TNF inhibitors (see FAD section 4.10). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).
NHS Professional 1	4	There were limitations to the quality of the research: A single short term RCT of golimumab against placebo is not a 'sufficient' evidence base to inform this decision.	Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9).

Role*	Section	Comment	Response
NHS Professional 1	5	The exact number of people who will be switched to golimumab or start this agent in preference to alternatives is unknown.	Comment noted. To the extent that number of patients impacts the budget, note that the Committee does not base its decision on the potential budget impact of a technology. The Committee takes account of how its advice may enable the more efficient use of available healthcare resources, as represented by estimates of incremental cost effectiveness (see Guide to the Methods of Technology Appraisal, section 6.2.14).
NHS Professional 2	1	We agree with the ACD: golimumab should not be recommended for the treatment of psoriatic arthritis.	Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity (based on the HAQ score results from the mixed treatment comparison and the data for radiographic progression), on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

Role*	Section	Comment	Response
NHS Professional 2	2	It is another anti-TNF inhibitor – it has not got a markedly different mechanism of action to the 3 anti-TNFs already licensed and approved by NICE. It has similar contra indications and cautions so would not allow different patient groups to be treated e.g. patients with co-existing moderate to severe heart failure. The recommended dose is 50 mg given once a month. The SPC states that in people who weigh more than 100 kg whose psoriatic arthritis does not show an adequate clinical response after three or four doses, the dose of golimumab may be increased to 100 mg once a month. The manufacturer's submission states that the cost of golimumab is £774.58 for a 50 mg pre-filled injection pen, and estimates an annual cost of £9294.96. People taking the 100mg dose would incur twice the annual cost and it is not clear how many would do so.	The Committee has recommended golimumab as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2). Although the evidence suggested that golimumab may be less effective in its anti-arthritic activity, on balance the Committee concluded that the evidence was not robust enough to confirm clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors (see FAD section 4.9). The Committee heard from the clinical specialists that they would be more likely to use a different TNF inhibitor than to increase the dose if the 50mg dose of golimumab failed to produce a response. The Committee concluded that it was uncertain of the extent to which the 100 mg dose would be used in clinical practice (see FAD section 4.6). TA 199 states that treatment choice among the TNF inhibitors etanercept, infliximab and abatacept should be based on cost (taking into account drug administration costs, required dose and product price per dose), with treatment initiated with the least expensive drug. The Committee concluded that golimumab would be considered an acceptable option for the treatment of psoriatic arthritis if used with same restrictions as included in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD section 4.14).

Role*	Section	Comment	Response
NHS Professional 2	3	We agree with the ERG concerns about the adverse event data presented for golimumab. No long-term adverse event data had been presented as the GO-REVEAL trial only lasted for 24 weeks. In addition golimumab is not included in the current BSR Biologic Registry and so there is no mechanism for monitoring the number of severe adverse events that might occur. We do not feel that the manufacturer can conclude that golimumab has a safety profile comparable to that of the other TNF inhibitors as they have not presented any long term safety data - there is still uncertainty about the long-term adverse event profile. In the mixed treatment comparison there were differences among the trial populations in disease severity and number of previously tried DMARDs (with many participants having received only one previous DMARD). We agree with the ERG comments that the trial populations were not precisely representative of the population with active and progressive psoriatic arthritis for whom TNF inhibitors are recommended in BSR guidelines and in NICE TA199.	Following consultation on the Appraisal Consultation Document, the Committee considered this additional evidence submitted by the manufacturer regarding adverse events associated with the use of golimumab for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis (see FAD section 3.8). It concluded that while there remains uncertainty about golimumab's long term adverse event profile, it had not been shown to be different from that of the other TNF inhibitors (see FAD section 4.10).
NHS Professional 2	4	Golimumab is not a cost effective treatment option: golimumab was 'extendedly dominated' by a combination of etanercept plus palliative care and golimumab was not found to be as effective as the key comparator, etanercept. There were limitations on the quality of the evidence. GO- REVEAL is one placebo controlled trial. There are no head to head trials with other anti-TNFs. It only had a very small number of participants (405) and it only lasted 24 weeks.	When each TNF inhibitor was compared with the next most effective alternative, all alternatives to etanercept were either dominated (infliximab) or extendedly-dominated (adalimumab and golimumab). As TA 199 had recommended adalimumab and infliximab alongside etanercept, the Committee considered whether golimumab was at least as cost effective as adalimumab and infliximab. The Committee noted the weaknesses of the evidence suggesting clinically important differences in the effectiveness of golimumab compared with the other TNF inhibitors. Given the weaknesses of the evidence suggesting lesser clinical effectiveness of golimumab compared with the other TNF inhibitors, and the estimates of golimumab's cost effectiveness compared with adalimumab and infliximab, the Committee concluded that the 50 mg dose of golimumab was acceptable when the criteria in TA 199 are met (see FAD section 4.12 and 4.13).

Role*	Section	Comment	Response
NHS Professional 2	5	The exact number of people who will be switched to golimumab or start this agent in preference to alternatives is unknown. It is unlikely that golimumab, even if approved as an alternative, would completely replace the other TNF-a inhibitors as there is more efficacy and long term safety data available for these agents.	Golimumab is recommended as an option for the treatment of active and progressive psoriatic arthritis in adults only if used as described for the TNF inhibitors in TA 199 and the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose (see FAD sections 1.1 and 1.2).

No comments:
Department of Health
Welsh Assembly Government
Pfizer