Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): Clinical effectiveness systematic review and economic model

Response to comments received during consultation

Summary of comments	Assessment Group response
MSD (response)	
1. The AG has not included the approved Patient Access Scheme (PAS) for golimumab in the report. We understand that updated analyses will be presented as an addendum to the Committee, however, we remain concerned that the initial analyses include an outdated price	The Assessment Group was advised by NICE that at the time of the assessment, the proposed PAS had not been agreed by the Department of Health. Subsequent to submitting the final assessment report, the PAS was approved and at NICE's request we have undertaken this additional analysis (see Addendum 1 to the AG report).
2. The AG criticise the MSD treatment pathway which compares surgery to TNF-α inhibitors yet describe a similar pathway (considering surgery and TNF-α inhibitors after conventional therapy failure and including a model state after TNF-α inhibitor failure similar to 'relapse management'	Our principal concern relates to the degree of severity of disease upon treatment failure and the assumed treatment pathway thereafter. The MSD model assumes that all patients receive i.v. steroids and imminently transit to surgery. As a consequence, the 10-year colectomy rate within the MSD model is around 70% in all treatment groups. This pathway and high colectomy rate is inconsistent with expert opinion received by the Assessment Group (~25%).
3. The AG has considered a subgroup of patients for whom surgery is not an "acceptable or preferable option". For these patients we believe that TNF-α inhibitors represent the only treatment choice once conventional therapy has failed	Surgery will not be necessary for, or acceptable to, all patients. We have separated out the analyses to allow for consideration of medical options alone. It should also be noted that if surgery truly was the only remaining option for patients following failure of conventional treatments, it would not have been either possible or ethical to undertake the trials of the biologics considered within this appraisal.
4. The AG has used indirect data at 32-52 weeks to inform modelling over the entire time horizon, which will overstate the benefits of adalimumab. It would be more appropriate to use data from the whole maintenance period (8-52 weeks), in-line with the design of the RCTs	We disagree with this position. If the data indicate a waning of treatment effect over time, as indicated by MSD, then this effect should if possible be reflected in the model. We agree however that the extrapolation of 1-year trial results over a longer time horizon is subject to considerable uncertainty. This is stated in the report.
5. The AG has incorporated a lower rate of adalimumab dose escalation (from every other week to weekly) than evidence suggests happens in clinical practice in the UK	We based our estimate on the ULTRA2 trial. We believe this is a reasonable source. Note that the Ferrante *et al* study is reported in abstract form only and we did not have access to it.
MSD (model proforma)	
1. The formula to calculate standard error from standard deviation is given as . It seems that /5 should be put inside of the radical symbol.	We agree – this is a minor programming error. The uncertainty surrounding the utilities will be inflated.

2. In the Arai publication there were 140 patients without complications and 156 with complications. For cells C177 and D177, it seems that alpha should be 156 instead of 140, and beta should be 140 instead of 156 (cf. Table 1 in the Arai publication). Furthermore, the reference year in the model was incorrect (2006 instead of 2005).	The reviewer is correct – the alpha parameter should have been 156 rather than 140. This has a negligible impact upon the model results and does not change the conclusions of the analysis.
3. It is understood that data were obtained from the UK IBD Audit report3; however the AG report refers to an oral presentation which did not provide the same information. In section 1.3.1ii UC section in the Audit report, causes of death included heart disease, respiratory disease, post-operative complications, and gastrointestinal bleeding. It is unclear whether the first two causes can be considered as excess mortality associated with surgery. This approach risks double-counting the background mortality. Furthermore, a beta distribution was assumed and the beta term should be the number of non-events. However, in the model, the sample size was used.	This is a minor programming error. The deterministic estimate is correct. The beta distribution is very slightly different due to the error (mean = 0.035 vs 0.036).
4. Costs are calculated using the lowest recommended dose, no justification is provided.	Refer to response to AbbVie comments 8 and 9.
5. The model assumes a gamma distribution if the number of patients in one health state is less than 340, otherwise a normal distribution. There is no explanation on the choice of such threshold or the assumption on the normal distribution. In the version of the model we received, there is no health state that has more than 340 patients (in the model that the evidence review groups disseminated), which means that a gamma distribution is always used.	This is to avoid an Excel calculation error if the sample size is too low. This is based directly on the supplementary material for the Briggs, Sculpher and Claxton book *"Decision modelling for Health Economic Evaluation"* 2006.
6. Premodel sheet, cell C196: the number of mg in an adalimumab vial should be 40mg. Table 72 of AG report: adalimumab dosing is 160mg, 80 mg, and then two 40mg doses during the induction phase. The latter doses are missing from the table in the report but are considered in the model.	As noted by MSD, these issues do not affect the execution of the model.
AbbVie	
1. The rate of dose escalation (27.4%) used in the model would not reflect the use of adalimumab according to the licence, which states that some patients who experience a decrease in their response may benefit from a dose increase. The proportion of patients receiving every week	The Abbvie model includes dose escalation at a rate of 21.49% from year 3 indefinitely. The rate in the AG model is slightly higher at 27.42% based on ULTRA 2 (based on text reported page 26 of the AbbVie submission). AbbVie's suggestion of a 0% dose escalation rate would not reflect the actual use of adalimumab.

(i.e. escalated) adalimumab maintenance should be zero (parameter 137)	
2. The model discontinues patients who were classified as non-responders in the clinical trial, which is not in line with the clinical trial protocol where patients who were non-responders could continue treatment. The indirect assumption in the model that patients who dose escalate would stop their adalimumab treatment does not take into account that patients could have achieved better efficacy.	We agree that this is not fully captured in the model. We did not have data to reflect the differential efficacy of patients who dose escalated and those who did not. As this is not a randomised group we would have concerns about its inclusion within the NMA. We would suggest that AbbVie provide NICE with estimates of how many dose escalated patients achieved response/remission but were not counted as responders within the manufacturer's response to the AG's data request.
3. The model assumes that all patients in the anti-TNF arm who discontinue therapy at week 8 due to non-response will receive conventional treatment and will only be able transition to surgery after receiving at least one cycle of conventional treatment. As discussed in the AbbVie response to the Assessment Report, it seems counterintuitive to require that all patients who failed anti-TNFs start with treatment they are intolerant to or treatment that has shown to be less effective than another treatment option, such as surgery. Also, allowing less than 1% of patients to proceed to surgery whilst on conventional treatment (which has shown to be less effective than surgery), appears counterintuitive and does not seem ethical or reflective of clinical practice	This is an assumption which is clearly stated as such (see AG report page 218). The proportion of patients getting to surgery is very uncertain – we based on estimates on Solberg et al – this leads to an overall surgery rate of about 30% of all patients over their lifetime. This is consistent with other estimates and expert opinion on the likelihood of surgery for this population received by the AG.
4. The model uses Solberg et al. as source of surgery rates. As outlined in the AbbVie response, Solberg et al. likely underestimates the probability of surgery given the differences in patient populations between Solberg et al. and the evaluation population.	We agree that this parameter is very uncertain. We used Solberg *et al* as it appeared to be the most relevant to the population under consideration. However, none of the studies included in the review were ideal. The estimates of colectomy rate within the model are similar to those provided by our clinical experts (~25%-30%).
5. The model assumes that patients may experience both transient and chronic complications related to surgery, and that transient complications can only arise during the same cycle as surgery, but not in subsequent cycles. Only chronic pouchitis is considered as a chronic surgery-related complication and uses a rate has been established among non-Western patients	The study reported by Arai *et al* shows a time series of when events occur. The vast majority occur in the first 2-years. We therefore assumed that all transient complications occur in the first cycle following surgery. As stated in the AG report, we did not undertake a systematic review of studies reporting post-surgical complications. We used the study reported by Arai as this was picked up in the

in a Japanese healthcare setting. No disutility is associated with surgery, a major procedure that requires hospitalisation, in the model.	MSD submission. We agree that other studies report different estimates of these complications. We could have included a disutility for surgery however we do not believe that this would substantially impact upon the model results.
6. The model only incorporates the cost of one surgical procedure for patients who proceed to surgical intervention	We agree that this may be under-costed for some patients who undergo more than one procedure. We did however include a sensitivity analysis in which the cost of surgery was doubled for all patients. This did not materially affect the model results.
7. As stated in the AbbVie submission, adalimumab reduced the risk by 30% for all cause hospitalisation compared to placebo and by 50% for all UC-related- hospitalisation compared to placebo. In the model a relative risk (RR) of 0.70 was used when comparing hospitalisations between adalimumab and placebo, based on the MSD NMA. It is acknowledged in the report that there is lack of clarity on the MSD NMA model, specifically, the methods whereby the results therein were obtained. It is also not clear to AbbVie if this figure relates to all-cause or UC-related hospitalisations.	We used the results reported in the MSD submission which relates to UC-related hospitalisation. Arguably the Feagan reference should be used however this was not included in the NMA by MSD. If the relative risk is assumed to be 50% this has a negligible impact upon the model results.
8. The model uses the lowest doses for induction and maintenance for the 5-ASA tablets.	The treatment regimens assumed were based on expert opinion (Prof Alan Lobo, chair of the UC NICE Guideline Development Group).
9. The cost in the model is based on the lowest cost preparation (Ipocol®)	If there is limited evidence of differential effectiveness between products, it seems sensible to use the least expensive.
10. The model does not incorporate the cost of stoma care.	The costs of managing UC following surgery are based on the estimates reported by Tsai et al. Note that not all patients would require stoma bags indefinitely as some would undergo IPAA (~60% based on our experts' judgement).
11. No costs have been allocated to the death state in the model.	We do not believe that it is standard practice to incorporate a cost of death. We also believe that where survival is not directly affected by the interventions, this would have a negligible impact on the cost-effectiveness of the interventions.
12. The mortality rate (qx) data in the model as it appears on the Premodel tab does not correspond to the source of the life expectancy table quoted in the Assessment Report	The reference in the report is inaccurate. We have used the 2012 England and Wales life tables in the model, as intended.
13. The source of the colectomy rate quoted on	This is an artefact of a prior model development

the Premodel tab (Gustavsson et al, AJG, 2007) does not correspond to the source in the Assessment Report (Solberg et al, Scan J Gastroenterol, 2009). The values used in the model do not correspond to Gustavsson et al., but to Solberg et al.	decision. We used estimates based on Solberg et al.
The transition matrices for all the anti-TNFs apply transition probabilities for the patients who transition to conventional treatment that correspond the same phase in the conventional treatment arm. The assumption is therefore e.g that patients who start on conventional therapy following anti-TNF treatment failure during induction will do so with the transition probabilities for conventional treatment as per maintenance 8-32 weeks, i.e. not the induction phase transition probabilities for conventional therapy. The maintenance phase transition probabilities for conventional treatment is applied to the same maintenance phase as anti-TNFs instead of the preceding phase.	Patients who fail on a biologic and subsequently receive conventional treatment relates to a population who has failed their induction regimen. Following dropout, the vector for the no response group (at maintenance) is applied. This would necessarily include various induction and maintenance therapies within each 6-month cycle. We do not believe that the model requires amendment.
Celltrion	
1. The report mentions and recognises biosimilars as part of the evidence base for infliximab. But, fails to include the anticipated lower cost of biosimilar infliximab (Remsima) in the health economic model . We believe that a lower price for biosimilar infliximab may have a significant effect on the ICERs which in turn will help the appraisal committee in their decision. Where colectomy is not considered to be an acceptable option the Assessment Group suggest that infliximab and golimumab are expected to be ruled out due to dominance. Applying the lower cost of biosimilar infliximab is likely to change this position.	No price was provided by Celltrion hence this option could not be included in the health economic analysis. The inclusion of an arbitrary price for Remsima would not be informative.
BSG (letter)	
1. The cost of conventional treatment, in the model, is very conservative.	See responses to AbbVie comments #8 and 9.
2. The modelling of response and maintenance therapy with anti-TNFs is opaque to us.	The modelling of response and remission is based on a NMA of the relevant trials. We did assume that patients achieving response and/or remission will continue to receive treatment until that benefit is lost. NICE did not stipulate a requirement for a “remission only” continuation rule. This may however be something that the committee is interested in.
3. The cost of surgery is grossly underestimated: most patients in the UK will undergo a colectomy with an ileostomy in the first instance.	We agree that the costs of the surgical procedures may be underestimated as this is applied only once in the model. We did however

	undertake a sensitivity analysis in which the cost of surgery was doubled and this did not influence the conclusions of the analysis. We believe that the estimated costs of stoma care provided by the BSG appear high and do not apply to all patients. We had assumed that some of these costs are included in the estimates reported by Tsai *et al*.
4. The care of teenagers with UC, who have received anti-TNFs by paediatricians, but who later become adults with UC is not addressed.	We believe that this is an issue for the Appraisal Committee to consider.
5. Sensitivity analysis. In our hands, the greatest change in the incremental cost per QALY were changes in the QOL in various disease states	We agree.
BSG (model proforma)	
1. Most patients who are eligible for anti-TNF therapy will not continue to take such for a year. A 10+ year time horizon is unrealistic. We anticipate 1/3-1/2 of patients who receive induction therapy will go on to receive maintenance therapy: the majority of failures will undergo surgery.	We adopted a lifetime horizon as this forms part of NICE's Reference Case. The model assumes that patients who do not achieve response at induction will discontinue biologic therapy. We believe that there is considerable uncertainty surrounding the colectomy rate – our experts suggest that this is likely to be around 25%-30% of this population.
2. Many patients (1/3-1/2) of those who are given maintenance will lose response during the first year: some may switch to another anti-TNF – but ultimately most will undergo surgery within 12 months of secondary failure.	The model includes discontinuation of those failing to maintain response/remission.
3. Of the patients who have a sustained remission to one year, we would anticipate many will stop therapy: patients with UC with sustained remission have a lower incidence of relapse than those who have recently flared.	We did not include this type of stopping rule within the analysis.
4. Most patients will not receive anti-TNF for more than a year, certainly not 10+ years, but a colectomy is a life-long state.	Most patients within the model have discontinued biologic therapy at 1-year (>75%).
5. Conventional treatment costs: We note mesalazine preparations used are the cheapest, and used at doses that is relatively low. This may concur with NICE, but does not reflect clinical reality: oral therapy for UC of this type would be 4-4.8g per day; the optimum dose of rectal therapy is 1g, not 250mg.	See responses to AbbVie comments #8 and 9.
6. All patients in the UK with this kind of UC will have 2- or 3- stage surgery.	See responses to AbbVie comment #6.
7. All these will have stoma-related costs for 6-12 months while waiting for the final operation.	See responses to AbbVie comment #10.
9. Anastomotic leaks and pelvic abscesses are common.	We based the incidence of post-surgical complications on Arai *et al*.

	The 2012 UK IBD audit reports similar rates - anastomotic leak rate = 10 out of 807 (1%) surgeries and intraabdominal sepsis rates = 43 out of 807 (5%).
10. Obstruction and or high-output stoma leads to admission	The model includes the costs of post-surgical complications and hospitalisations based on Tsai *et al*, costed using NHS Reference Costs.
11. Most/all patients used large amounts of loperamide to manage their stoma and or their pouch.	We would assume that these costs would be included in the estimates reported by Tsai *et al*. Note also that loperamide is relatively inexpensive.
12. 20-30% of patients undergoing colectomy will keep their stoma in the medium to long term because preference, risk of impotence/retrograde ejaculation, reduce fecundity or for surgical reasons.	See responses to AbbVie comment #6.
13. The real cost of Biosimilars is not known: experience form Hungary is that they are substantially cheaper than the originator drugs.	We were unable to include biosimilars in the analysis as the price remains unknown.
14. The data used is very limited and questionable: the QoL of patients after surgery is not a good as the model suggest.	We examined the impact of different sources of HRQoL within the model. This did change the model results but not the overall conclusions. Multiple EQ-5D studies report high HRQoL following surgery. In the absence of post-surgical complications, our experts concurred with this view.
HIS	
1. It is important that the Executive Summary is clear and easily understood when read on its own. On page 17 it refers to patients classified as responders at the end of the induction phase and also patients classified as being in remission at the end of the induction phase. The Executive Summary needs to state clearly what is meant by responders versus those being in remission at the end of the induction phase.	The definitions of response and remission are given clearly in the main body of the report.
2. On page 17, what is meant by the sentence "For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant".	This means that the difference in the proportion of patients who were induction responders between groups was not statistically significant at the conventional 5% level.
3. It would also be useful in the Executive Summary to explain what happened to the other treatment the patients were receiving before being randomized to the biological therapy of placebo. When patients come in to these studies, they are classified as failure or conventional therapy. Presumably, the conventional therapy was largely steroids and Azathioprine. Was the conventional therapy discontinued as it was not working, or was it continued in part or whole?	Full details are provided in Chapter 5 of the report.

4. In the Executive Summary and several other points in the document, the term "dominance" is used. For example, in the sentence "ruled out due to dominance". What does this mean? It sounds like some special epidemiological or economic analysis term. It is important that those words are not used without clear explanation as to their meaning.	This is conventional terminology in health economic evaluation.
5. On page 28, it states "Treatment using immune-modulatory therapy will be started at the same time as oral corticosteroids". I do not think this is the case. Patients with ulcerative colitis will often receive an initial course of steroids and sometimes one or two further courses of steroids before being commenced on maintenance Azathioprine. The two are not necessarily started together.	This treatment pathway was based on expert opinion informed by the chair of the NICE GDG.
6. In the economic analysis, it seems to be assumed that biologic treatment will be life-long but evidence in Crohn's disease suggests patients may be successfully maintained in remission after a period of biological therapy and on withdrawal. There is clearly no evidence regarding this in ulcerative colitis, which makes predictions of long-term costs inaccurate.	It may be possible or even preferable to withdraw biologic treatment after some period of time. However we were not asked to consider this type of discontinuation rule nor was there any evidence to support it. This is not a matter of inaccuracy. It is an unknown.
7. I think the prevalence of pouchitis following IPAA is under-estimated – they state 5% but some data suggests up to 50%.	There are higher rates reported in some studies. Arai reported an estimate of 16/296 (5.4%). This is what we used. We did examine a sensitivity analysis in which this probability was doubled.
8. There will be a group of patients who may not consider surgery acceptable. The document does not offer solution for these patients.	The health economic analysis is undertaken for two groups – one in whom colectomy is acceptable and one in whom colectomy is not an option.
9. The document provides useful information on the costs of the biologics versus other treatments but does not seem to come to any conclusion as to whether the biological therapy should be approved for use or not. In order to come to a conclusion on that, it would be helpful to include a comparison of the cost-effectiveness of the biological therapy in ulcerative colitis contained in this document with that already calculated for its use in Crohn's disease. This would help see the cost-effectiveness in perspective.	The AG is not charged with making recommendations on the use of health technologies within the NHS.
UKCPA	
1. Mayo Score versus Truelove and Witts scoring will cause an issue correctly identified in the report. Currently the NHS would not have the capacity to do repeat endoscopies to support frequent Mayo scoring. This may cause an issue	The model is based on full Mayo scores as reported in the clinical trials. It is not possible to re-evaluate the model using partial scores.

when trying to distinguish between patients with response and pat in remission after induction. Consider using the Partial Mayo scoring as assessment tool .	
2. In view of the new NICE recommendations it needs to be made clear what acceptable or preferable option for biologics instead of surgery involves.(7.1) Surgery may be considered as an option for patients with UC for a number of indications including due to complications of disease, perceived risk of or identified dysplasia/neoplasia or due to lack or loss of efficacy of medical treatments. For a proportion of patients without emergency symptoms, surgery may not represent an acceptable treatment option	This is a matter for the Appraisal Committee to consider.
3. From the 5.3 discussion it is difficult to distinguish between the effects of the biologics. The text is slightly confusing as multiple parameters discussed a short paragraph. i.e. pt in remisson after induction seem to adalimumab has the highest probability for staying in remission, but this may be irrelevant if only a small number of patients respond to adalimumab in the first place.	The report includes the reported outcomes of the individual trials as well as a description of the NMA which is based on conditional probabilities of response and remission.