National Institute for Health and Care Excellence
10 Spring Gardens, London, SW1A 2BU

17th December 2014

Dear Bijal,

RE: Vedolizumab for treating moderately to severely active ulcerative colitis [ID691]

MSD thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD). We welcome the addition of new treatment options for patients with moderately to severely active UC who have only recently provisionally gained access to any NICE-approved biologic treatments (once conventional therapy has failed or in cases where it is contraindicated or cannot be tolerated) through the Multiple Technology Assessment of the three TNF-alpha inhibitors, Remicade, Simponi, and Humira.

However, although we understand that the wording in section 1.1 of the ACD is not meant to recommend a specific treatment pathway (in terms of the order in which biologic therapies are to be used); we are concerned that the wording could be seen to imply this. Through moving the first bullet point ("the person has not had a TNF-alpha inhibitor or") later on in the recommendation, this could resolve this potential for misinterpretation and we believe would not change the intent of the committee.

We also believe that the current wording of the recommendation may prejudice against patients who have previously received Remicade for the management of acute severe UC (in line with Technology Appraisal Guidance 163) as is it not clear whether they would then be able to receive vedolizumab for any future treatment of ongoing moderately to severely active UC (not acute).

Through reviewing the material submitted by the manufacturer of vedolizumab and the Evidence Review Group's appraisal of that material, we have noted three key inaccuracies which may impact the cost-effectiveness estimates which have been considered by the appraisal committee:

1. The approved Patient Access Scheme for golimumab has not been included in the manufacturer's cost-effectiveness model
2. The cost-effectiveness model includes a number of induction doses for vedolizumab which is not consistent with its marketing authorisation
3. The network meta-analysis is not a credible reflection of available data from randomised controlled trials and has been inappropriately applied in the cost-effectiveness model

Further detail on these three points is provided overleaf, though in summary, the cost-effectiveness results presented by the manufacturer of vedolizumab may not be an accurate reflection of the true cost of vedolizumab in both the TNF-alpha inhibitor-naïve and TNF-alpha inhibitor-failure populations.

Finally, please note that MSD has been omitted from the list of commentator organisations in the ACD.

Kind regards,

1. Omission of golimumab Patient Access Scheme in cost-effectiveness model

The manufacturer of vedolizumab made their submission on the 25th July 2014, which is after the date on which the Patient Access Scheme (PAS) for golimumab was approved by the Department of Health (decision communicated on 16th July 2014). Surprisingly, the PAS for golimumab was not applied in the model although according to the final scope issued by NICE "The availability of any patient access schemes for the comparator technologies should be taken into account."

The golimumab PAS gives the opportunity for the NHS to access the 100mg dose at the price of the 50mg dose. Consequently, the number of golimumab doses used in the induction period decreases from six to three and the total drug price for induction with the PAS is £2,289 not £4,578. MSD have explored the impact of including or excluding the golimumab PAS in our own model (developed for the NICE UC MTA) and we would expect the same amendments in the vedolizumab model to have implications on the cost difference between vedolizumab and golimumab. According to Table 103 in the manufacturer's submission, the total incremental difference between vedolizumab and golimumab is £1,312. By applying the PAS price for golimumab, the total cost over 10 years for the golimumab arm in the model would be less than that of vedolizumab. Therefore, it follows that golimumab would not be dominated by vedolizumab.

2. Number of vedolizumab induction doses in cost-effectiveness model

In the manufacturer's cost-effectiveness analysis, vedolizumab treatment in the induction period is assumed to be administered as a 300mg intravenous infusion at weeks 0 and 2. According to the submission, this dosing assumption is based on the GEMINI I dosing regimen. However, the EMA marketing authorisation for vedolizumab recommends that 300mg is given at 0, 2, and 6 weeks. MSD strongly believes that assumptions adopted in cost-effectiveness models should reflect the way the medicine will be used in UK clinical practice. Additionally, according to the 'Guide to the methods of technology appraisal 2013': "6.1.12 The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics". By increasing the number of vedolizumab infusions in the induction phase to three, the overall drug costs for vedolizumab would be expected to increase.

3. Use of network meta-analysis data in cost-effectiveness model

We do not believe that the network meta-analysis (NMA) performed by the manufacturer is appropriate to support the cost-effectiveness modelling for a number of reasons.

a) Inconsistencies between effectiveness estimates from NMA and trial data

First, we note that the NMA data have been applied only in the TNF-alpha inhibitor-naïve population while trial data has been used in the other populations. This approach is inconsistent and may be misleading due to the discrepancies between the findings of the NMA compared to the GEMINI I data

for vedolizumab which suggests that there may be poor convergence of direct and indirect evidence in the NMA (Table 1).

Table 1: Efficacy outputs from manufacturer NMA and GEMINI I trial

Response – Induction			**Remission – Induction**		
Treatment	NMA	Trial	Treatment	NMA	Trial
Vedolizumab	**62.4%**	**53.1%**	Vedolizumab	**30.2%**	**23.1%**
Infliximab	68.2%		Infliximab	33.4%	
Adalimumab	49.6%		Adalimumab	15.1%	
Golimumab	57.0%		Golimumab	25.8%	
Placebo	**34.3%**	**26.3%**	Placebo	**8.9%**	**6.6%**
Response - Maintenance			**Remission – Maintenance**		
Treatment	NMA	Trial	Treatment	NMA	Trial
Vedolizumab	**80.6%**	**65.3%**	Vedolizumab	**57.5%**	**45.8%**
Infliximab	56.7%		Infliximab	31.7%	
Adalimumab	51.1%		Adalimumab	42.4%	
Golimumab	60.4%		Golimumab	39.0%	
Placebo	**44.0%**	**26.6%**	Placebo	**27.2%**	**19.0%**

b) Alternative perspective on relative effectiveness estimates from NMA

MSD has incorporated the results from the GEMINI I trial into the NMA that was submitted by MSD as part of the NICE UC MTA.

The NMA presented by Takeda stated that for the TNF-alpha inhibitor-naïve population, in induction, infliximab was most effective, followed by vedolizumab, golimumab, and then adalimumab (ranking was the same for clinical response and clinical remission). In maintenance, vedolizumab was found to be most effective, followed by golimumab, adalimumab, and infliximab.

While the updated MSD NMA (fixed effects model) found that for induction the ranking of therapies was the same, for maintenance, infliximab moves from being the least effective therapy at maintaining remission (as stated by Takeda) to being the most effective (more effective than vedolizumab) (Table 2).

Table 2: Vedolizumab relative effectiveness estimates from MSD NMA updated with GEMINI I data

Vedolizumab vs.	**Remission – Maintenance**	
	Updated MSD NMA	**Takeda NMA**
Adalimumab	1.40 (0.27 to 7.56)	2.14 (0.81 to 5.82)
Infliximab	0.81 (0.16 to 3.92)	2.93 (1.03 to 8.46)
Golimumab	1.27 (0.27 to 5.91)	2.10 (0.90 to 5.32)
Placebo	2.34 (0.50 to 11.12)	3.67 (1.85 to 7.88)

c) *Inconsistencies between transition probabilities derived from NMA and trial data / lack of clarity around transition probabilities*

The inappropriateness of using the NMA to support the TNF-alpha inhibitor-naïve population modelling is further apparent in the transition probabilities that are applied in the cost-effectiveness model.

First, it is not clear how these have been derived from the NMA as the equations used were not made available for review (they were included in an appendix to the manufacturer submission). Due to this lack of transparency it is not clear whether the magnitude in the differences between transition probabilities is logically related to the magnitude in the differences between the effectiveness of each biologic therapy according to the NMA.

Secondly, there are inconsistencies between the transition probabilities derived from the NMA and those derived from the trial data (Table 3). We note that the manufacturer's model itself states that the NMA data are inappropriate to use for the comparison between vedolizumab and conventional therapy as head to head data exist ("NOTE: Head to head data exist and should be used for comparisons between vedolizumab and conventional therapy"), however, the ICER produced using this inappropriate setting was presented to the appraisal committee as the base case for the TNF-alpha inhibitor-naïve population. Amending the data set that is used has a large impact on the cost-effectiveness estimate, highlighting the considerable uncertainty arising from using the NMA.

Table 3: Transition probabilities for vedolizumab derived from manufacturer NMA and GEMINI trial

	NMA	**Trial**
M to R	0.200	0.087
M to MS	0.181	0.287
MS to MS	0.711	0.817
MS to M	0.281	0.175

M, mild; MS, moderate severe; R, remission