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

27th January 2014

Dear Bijal,

RE: Vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease [ID690]

MSD thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD). MSD believes that the preliminary recommendation by the appraisal committee is appropriate given the evidence presented. Having reviewed the material submitted by the manufacturer of vedolizumab and the Evidence Review Group's appraisal of that material, we would like to reiterate the limitations in the handling of clinical data, and emphasise the following:

1. When Targan *et al*. 1997 is included in the manufacturer network meta-analysis (NMA) for induction (Table 1, p.16 of ACD), infliximab is associated with odds ratios (ORs) for clinical response and clinical remission vs. placebo which are ~10-fold higher than the ORs for vedolizumab or adalimumab vs. placebo for the same outcomes. However, these ORs were not applied in the original or the updated manufacturer model. Infliximab data were instead derived from ACCENT I.

   The probability of achieving response/remission with infliximab has likely been underestimated in the manufacturer model as a result of using data from ACCENT I (Table 1). Given that the difference in the ORs of response between vedolizumab vs. placebo and adalimumab vs. placebo is 0.7 and the corresponding difference in the probabilities of response is 7.42%, it seems implausible that the probability of response with infliximab should be only 63.50% (given that the OR for infliximab vs. placebo is 10-fold higher than that of adalimumab vs. placebo). In addition, the probability of remission with adalimumab is higher than that estimated from ACCENT I for infliximab, despite the OR of remission for infliximab vs. placebo being ~10-fold higher than for adalimumab vs. placebo.

Table 1: Comparison of ORs and probabilities of response/remission

	Response (week 6)		Remission (week 6)	
	OR from NMA	Probability	OR from NMA	Probability
Conventional therapy	1.0	38.33%	1.0	15.63%
Vedolizumab	1.8	53.01%	2.9	34.89%
Adalimumab	2.5	60.43%	2.3	29.92%
Infliximab	25.0	*63.50%* *	26.0	*34.50%* *

* derived directly from ACCENT I, not NMA.
Adapted from Table 7.3.1.2 in the manufacturer submission, error in infliximab remission probability corrected as per manufacturer response to clarification questions.

   Consequently, it would be useful to understand the impact of using probabilities of response/remission derived from the NMA for *all* comparators on the relative cost-effectiveness of these therapies.

There are two statements within the ACD that could be interpreted as being contradictory regarding the manufacturer's use of NMA data (emphasis added by MSD):

- Section 3.45: "For the comparisons between vedolizumab and the other biological therapies (infliximab and adalimumab) in the population who had not had a TNF-alpha inhibitor before, *the clinical parameters in the company's updated model were wholly derived from the network meta-analyses provided in the company's clarification response* (see section 3.52). These superseded the original analyses in which the clinical parameters for infliximab and adalimumab were derived from the network meta-analyses and those for vedolizumab (and conventional non-biological therapy) were derived from GEMINI II and III."
- Section 3.46: "The company estimated the efficacy of each treatment by estimating odds ratios using response and remission data from the network meta-analyses (the population who had not had a TNF-alpha inhibitor before) or from pooled trial data (the mixed population and the population in whom TNF-alpha inhibitor treatment had failed). In the population who had not had a TNF-alpha inhibitor before, *infliximab data were derived from ACCENT I, separate from the network meta-analysis.*"

Kind regards,

[redacted]
Senior HTA and EBM Manager