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**National Institute for  
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Dear [REDACTED],

**Re: Single Technology Appraisal –  
Botulinum toxin type A for the prophylaxis of headaches associated with  
chronic migraine**

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have now had an opportunity to take a look at submission received on the 10 October 2011 by Allergan. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 16 November 2011**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under '**commercial in confidence**' in turquoise, and all information submitted under '**academic in confidence**' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Helen Starkie – Technical Lead ([Helen.Starkie@nice.org.uk](mailto:Helen.Starkie@nice.org.uk)). Any procedural questions should be addressed to Kate Moore – Project Manager ([Kate.Moore@nice.org.uk](mailto:Kate.Moore@nice.org.uk)) in the first instance.

Yours sincerely

Helen Knight  
Associate Director – Appraisals  
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

**Clarification on manufacturer's submission: clinical and cost effectiveness**

- A.1** Page 160, section 6.5.6 states that "...quantities of resources are taken from the International Burden of Migraine Study (Section 6.4.6, page 148)....", however section 6.4.6 (on pages 149-150) refers to Blumenfeld 2011 (Cephalgia) but does not give any data on resource use by frequency of headache bands.
- a) Please explain where the data on resource use by health states, used in table 6.17, come from (if from the IBMS, should the data be labelled as academic in confidence)?
- b) The Blumenfeld 2010 paper from the IBMS refers to hospital visits (in addition to neurologist visits) in table 6, but refers to hospitalisations in the text on page 10. Please clarify whether the table is really referring to admissions, and similarly, in tables such as 6.17 and 6.18, whether the term hospitalisations refers to hospital admissions.
- A.2** It is stated that at present only 17% of people with chronic migraine are seen in specialist care. Please provide data on this, including how often patients are seen and how long each visit lasts.
- A.3** Please provide the justification for why the number of injections has been set at between 31 to 39, and in 7 areas.
- A.4** Please explain whether botox therapy for chronic migraine is an evolving technology?
- A.5** Please provide the baseline characteristics for those people recruited into PREEMPT (in the pooled population) who had received 3 or more prior oral preventative drugs.
- A.6** Please provide a graph of the observed (from mapping from MSQ) and predicted EQ-5D scores in the pooled data for the population in the decision problem.

- A.7** Please clarify why the MSQ was not used in conjunction with the HIT in the pooled analysis to derive utilities for the economic model.
- A.8** Please provide the percentages of people having clinically meaningful (taken to be 10.9 for RR; 8.3 for RD and 12.2 for EF) MSQ responses for each of the three domains as done for the HIT results in figure 5.12 of the submission, and a graph as per figure 2a (for HIT 6) of the paper by Lipton et al (Neurology 2011;77:1465-72) showing the percentages of patients with clinically meaningful MSQ results for the same time periods.
- A.9** Please check table 6.24. Life years should be the same.
- A.10** Are there data on medicines overuse in the trial by arm? If so, please provide these data.
- A.11** In table 6.27, there is an administration cost of £267 for placebo: the administration costs are greater for the non-Botox arm than for Botox. Please explain this.
- A.12** In PREEMPT 1, there were significant differences in the baseline variables (table 5.7) with p values of 0.023 for mean headaches episodes; 0.006 for mean migraine episodes; and 0.022 for headache hours.  
a) What is the likely explanation for these p values?  
b) In the pooled data (table 5.9) the p values for some variables are smaller than in tables 5.7 and 5.8. Please explain this since pooling would be expected to dilute the significance seen in table 5.7, not increase it.
- A.13** Please provide details of the observed distributions of baseline variables in the UK sample in the CM subgroups in the PREEMPT 1 and 2 trials (tables like 5.7 and 5.8 for the UK sample only would be helpful).
- A.14** Please provide a table similar to table 5.9 for participants relevant to the decision problem – that is, only CM patients who have been unsuccessfully treated with 3 or more oral prophylactics.
- A.15** Please justify the time horizon of 2 years (which is contrary to the NICE methods guide which requests a lifetime horizon for the economic

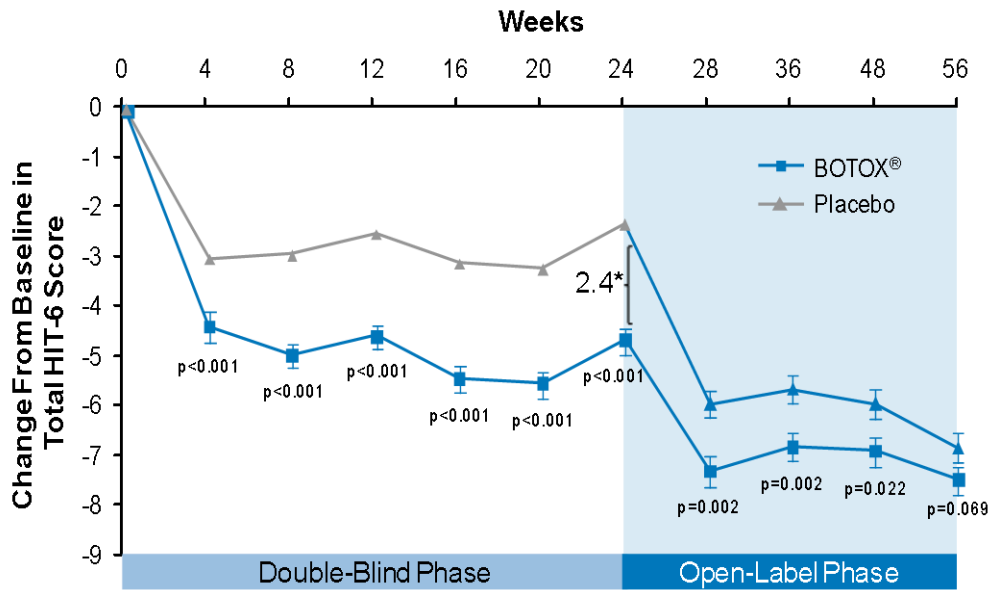
model). On page 70 it was noted that the population in PREEMPT 1 had been “severely impacted by their headaches with means of >20 years of frequent headaches”. Would that not suggest that a 20 year time horizon should be used as one of the scenarios?

**A.16** There was a statistically significant reduction of secondary efficacy end points favouring Botox (a reduction of 0.5 migraine days) in the PREEMPT 1 trial. Please clarify the exact statistical test undertaken in the pooled data and explain why it is expected that this difference is clinically significant.

**A.17** In the Markov Model standard of care, the cycle probability of death is the same from week 0 to week 48 over 365 days. Please clarify why it is expected that there is the same cycle risk of death in the placebo arm from 0 to 48 weeks and why this assumption was not made over the 2 year time horizon?

**A.18** a) The model applies the negative stopping rule after 2 cycles, i.e. Botox injections at baseline and 12 weeks. Given that most benefits occur after the first injection, please explain what would be the impact of applying the stopping rule after one injection?

b) In figure 5.12, reproduced below, there is a marked improvement in the former placebo group after their first injection of Botox. This is similar to the former Botox group after their first injection. However there is also a marked improvement in the former Botox group. What is the likely explanation for this?



**Figure 5.12:** Mean change from baseline at week 24 for HIT-6 results in pooled phase 3 studies (ITT population) (Aurora, 2009b)

**A.19** EQ-5D utility scores are known to exhibit a ceiling effect, where a large proportion of subjects rate themselves in full health with a utility score of 1, and hence the data can be interpreted as being bounded or censored at 1. The ERG believes that ignoring the bounded nature of the EQ-5D will result in biased and inconsistent estimates. Please clarify how the upper censoring limit of 1 of the EQ-5D was taken into account in the mapping?

**A.20** The mapping model used in the submission is an OLS. The squared terms (quadratic terms) are designed to pick up non-linearities in the relationship between dimension scores and the EQ-5D index was also investigated but not retained in the final model. Please clarify why the OLS was used instead of an additive model (for instance censored least absolute deviations (CLAD) or tobit model) which imposes no restrictions on the relationship between dimensions?

**A.21** The ERG explains that interaction terms are important since there is evidence from other measures that dimensions are not additive. Please clarify why the interaction between MSQ and HIT was not investigated in the pooled data?

- A.22** With reference to the low drop-out rate: were patients told at recruitment that there would be an extension study in which they would all get botox?
- A.23** In the SMC guidance, there is mention of Botox being given at 18 week intervals in year 2. Is there any evidence that frequency of injections can be reduced without losing effect?
- A.24** IBMS reports that 11.5% of people with CM have fibromyalgia. Please explain why these people were excluded from the PREEMPT trials?
- A.25** Please clarify whether the IBMS data give EQ-5D by the same headache bands as in the modelling?
- A.26** The PREEMPT trials used 31 to 39 injections. Do the additional 8 injections relate to the “follow-the-pain” method described in an abstract by Aurora and colleagues (P05.280) at the annual meeting of the American Academy of Neurology? There does not seem to be any reference to “follow-the-pain” in the submission. Please provide further information on the marginal benefits of the extra Botox if available.

***Clarification on manufacturer’s submission - wording***

- B.1** Page 7 says “two 56 week placebo controlled clinical trials” but duration of the trials was only 24 weeks.
- B.2** Page 15 – “difference between the two patient groups still significant at one year” – but this was not so in the HIT-6 results, where  $p = 0.069$ .
- B.3** On page 74, first sentence of last paragraph should refer to table 5.16 not 5.14.