Author's response to reviews

Title: Clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review and economic evaluation

Authors:

David J Moore (d.j.moore@bham.ac.uk)
Yaser Adi (y.adi@warwick.ac.uk)
Martin J Connock (m.j.connock@bham.ac.uk)
Sue Bayliss (s.bayliss@bham.ac.uk)

Version: 2 Date: 2 June 2009

Author's response to reviews: see over
Referees Comments and Authors Responses

REFEREE 1: P CHANSON

Major comments:

1- Page 12. The paragraph on GH levels needs to be discussed in light of the interference of pegvisomant with GH assays, that may explain that some results may be artefactual due to the absence of discrimination between the drug and GH with some assays; moreover, many variations in GH levels observed during the use of this drug are likely explained by the hook-effect related to the amount of pegvisomant, (Paisley et al. Eur J Endocrinol 2007). All these points need to be explicitly indicated in the paper as it has major consequences on the use of GH assays in patients with acromegaly treated with pegvisomant (GH assays are probably not to be recommended) and also on the interpretation of the course of GH levels during the treatment.

Response: On page 12 we have now inserted the sentence
“PEG may interfere with commercial kit-based immunoassays for GH Paisley et al 2007[25], and this could impact on the quantitative interpretation of published results”

2- Pages 15 and 16. Even if these studies were published after the end of collection of the studies by the Authors there are now data on QoL during pegvisomant which may help to refine, if useful, the model

Response: We have updated our search for QoL studies. Although, as mentioned by the referee, there are new QoL publications we have found none that provide utility data for patients receiving PEG and consequently they do not provide useful information that might improve or refine our economic analysis.

3-Page 16. Concerning the non-responders and the fact that it is « unrealistic that non-responder patients would persist with pegvisomant… », it must be kept in mind that even if not normalized, some patients (which proportion ?) may greatly benefit from treatment and would ask to continue the treatment for long time…This points to the fact that in the treatment of acromegaly, particularly in cost-benefit analysis studies, one need to take into account the patients who are clearly improved by the treatment…even if not « normalized » in terms of hormonal control…pushing, in some cases, to continue what appears to be an insufficiently active treatment.

Response: The economic analysis took a “perfect drug” perspective and assumed all patients were responders, therefore the problem mentioned by the reviewer does not arise.

4- Page 19. With regard to our previous remarks in §1, the sentence « Increased GH incompletely blocked by PEG might exacerbate… » is too speculative and needs to be amended. This sentence might also lead the Reader to think that the Authors did not understand the mechanism of action of the drug : indeed, whatever the levels of GH, as soon as the GH receptor is blocked, there is no reason to have effects related to GH…even if GH levels are high.

Response: We have now omitted this sentence.
Minor comments:

1- Figure 5. If data were extracted from the meta-analysis papers of Dekkers et al. J Clin Endocrinol Metab 2008 and/or Holadaway et al. Eur J Endocrinol 2008, this needs to be acknowledged.

Response: This data was assembled and supplied by Professor Paul Stewart and Dr Andy Bates who are acknowledged in the acknowledgements section.

REFEREE 2: S MELMED

1- Figure 4. These survival curves do not take into account the toxic effects of the drug--including longterm liver abnormalities which will impact morbidity longterm, as well as cost. Furthermore what is missing is a curve depicting alternate therapies--eg surgery or somatostatin analog which will likely yield a more favorable curve, given the side effects of PEG.

Response: A curve for survival after various alternative therapies would be interesting however would not be relevant as an appropriate comparator for the decision problem addressed in the economic analysis which specified the use of pegvisomant (according to the European licence) for patients in whom the alternative therapies were unsuitable or unsuccessful (failed to normalise IGF-1 levels). We have inserted the following sentence in the introduction so as to clarify this point.

“In Europe, PEG is licensed for patients who have had an inadequate response to surgery and/or radiation and in whom an appropriate medical treatment with somatostatin analogues did not normalise IGF-1 concentrations or was not tolerated[5].”

2- Please address side effects more comprehensively eg the lipohypertrophy caused by the drug. See Bonert et al in JCEM 2008.Also, the hepatitis question requires far more critical analysis, as well as the potential for continued (or accelerated??) tumor growth in the longterm. This leaves a poor balance to the review which is otherwise excellent.

Response: We have:
[a] commented further on side effects and mentioned and referenced the issue of lipohypertrophy; “Other side effects include headache, injection-site reactions, flu-like syndrome and recently injection-site lipodystrophy sufficient to cause discontinuation has been reported [64].”
[b] inserted the phrase “however continued vigilant monitoring of tumour size is mandatory during PEG treatment” to address the issue of tumour growth;
[c] inserted the sentence “This means monitoring for possible liver damage is a necessity during long term administration of PEG” to address the issue of hepatitis.

REFEREE 3:

This referee did not make any comments requiring a response.