Author's response to reviews

Title: Pregabalin versus gabapentin in the management of peripheral neuropathic pain associated with post-herpetic neuralgia and diabetic neuropathy: A cost effectiveness analysis for the Greek healthcare setting

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Author's response to reviews:

To:

BMC Neurology

Dear Sirs

First of all, we would like to thank you and the reviewers for the time devoted to the review process of our manuscript and for the useful comments that emerged. In the paragraphs that follow you can notice that we have made extensive revisions to the manuscript in an effort to address all comments raised, based on our understanding of the changes requested. Specifically:

In response to the Editorial Requirement:

A statement that says that the manuscript was exempt from needing ethical approval was added as an acknowledgment

In response to the Reviewers' Comments:

Reviewer: Cory Toth

Minor Concerns

The model used was rather simple and based upon physician surveys. It is not clearly stated in the Discussion that there are certainly limitations of such a simplistic approach. Many comparable studies would use actual health care
A specific passage discussing the above mentioned comment was added in the limitations section of the manuscript.

Posttreatment pain score mean values were 4.1 for pregabalin and 4.8 for gabapentin – was this a significant difference? What about the reduction in days with moderate to severe pain?

Both differences were found statistically significant (at the 0.05 level) by the simulations. This was added in the “Results” section.

It is not stated in the Results if the QALY gain was significant either.

Same as per the above comment.

There should be some discussion by the authors regarding what is an efficient QALY gain. Is 20,000 euros acceptable? This is controversial and depends upon many complex considerations and is variable between counties, but $40,000 USD for 1 QALY is considerable. More discussion about the relevance is required.

Taking into account the above mentioned comment, the paragraph discussing the “cost per QALY gained” in the “Discussion” section was enriched, both in terms of extent as well as with regards to referenced papers.

It should be noted that according to latest Greek legislation, the reimbursement of new healthcare technologies in Greece is influenced by the reimbursement status in other European countries and the assessment outcome from reputable health technology assessment bodies such as NICE. It could be therefore accepted that the willingness to pay is determined by the thresholds used by other assessment authorities and as such, their threshold could be used as a valuable guide in alliance with the GNI calculations.

Reviewer: Shekoufeh Nikfar

1- Please provide: The reason that authors consider DPN and PHN but they didn’t mention other indications of gabapentin and pregabalin to control pain like fibromyalgia.

Pregabalin is indicated for both peripheral and central neuropathic pain whereas gabapentin is only indicated for peripheral neuropathic pain. Comparison of the two drugs therefore is focused on peripheral NeP. EMEA guidance also states that efficacy demonstrated in #2 models (e.g. PHN, DPN) in well controlled trials supports efficacy in peripheral neuropathic pain as a broad entity (The European
Agency for the Evaluation of Medicinal Products: CHMP/EWP/252/03). DPN and PHN are considered the most representative causes of peripheral neuropathic pain which is why scientific focus lies mainly on painful diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN), extrapolating any outcomes on other causes of NeP. Although pregabalin has the indication of fibromyalgia in the US, it is important to point out that neither gabapentin nor pregabalin have the fibromyalgia indication in Europe and therefore their cost-effectiveness in this patient population cannot be measured.

2- Please demonstrate the model figuratively. It will help it to be clear.

A schematic demonstration of the model was added in the manuscript (Figure 1). Additional information was also added in the study methods in order to enhance clarity.

3- In sensitivity analysis: There is more important variable in cost that should be considered for consistency. The variation of cost because of prescribing divided doses of drugs should be considered.

This comment underlines a limitation of the analysis, due to the design of the model. A specific passage was added both in the methods section (under the “health care resource and medication costs” heading) as well as in the limitations of the analysis. The latter states the limitation and underlines that a similar approach was used in other adaptations of the model in different health care settings.

4- I recommend the following article that has been published recently in same perspective to compared and discussed with this article: The effectiveness and cost-effectiveness of pregabalin in the treatment of diabetic peripheral neuropathy: A systematic review and economic model. International Journal of Pharmacology 2012; 8(6): 490-495.

The recommendation was followed and a specific passage (along with the corresponding reference) was added in the “Discussion” section.

5- Authors have claimed that “generic preparations of gabapentin were not included in the analysis due to their low penetration in the Greek healthcare market”. If at the same time generic preparations of pregabalin is available in market according to economic evaluation grid the result will show that use of gabapentin is dominated. Please explain this complexity.

Indeed the economic evaluation would produce more favorable results should generic preparations had been taken into consideration. However, generics of pregabalin do not exist in the Greek market, as the data exclusivity patent and the compound patent for pregabalin are still valid. Moreover, based on Greek legislation, generics of an original active substance are not legally allowed to
enter the market as long as the compound patent is in force, therefore those calculations were not included in the analysis.

Overall, based on our understanding of the comments raised, a special effort was given to address all of them as thoroughly as possible without extending the length of the manuscript to a great degree. Needless to say, we do remain at your disposal, should any further changes be deemed necessary.

Sincerely yours,

Elli Vitsou,

on behalf of the team of authors