SHIRE PHARMACEUTICALS - COMMENTS ON ASSESSMENT REPORT (TA111) JULY 2010

The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model. Assessment Report sent 07 July 2010

Shire is grateful for the opportunity to respond to the above mentioned assessment report. We find the report to be both unsatisfactory and incomplete for the purpose intended and list our reasons below.

1. **PenTAG themselves describe limitations of their review**

Quotes from the report to support these limitations:

- Section 1.4.3. The results are highly uncertain and very sensitive to changes in several model assumptions and parameters.

- Section 1.4.3. There should be no initial presumption that the model from the independent review group is somehow more valid or reliable than the others. The authors suggest that 4-5 months to develop the PenTAG model is inadequate compared with the time available to the manufacturers, with their additional access to trial data.

- Section 1.5.2. The model should be regarded as explorative for assessing the cost-effectiveness of drug treatments

- Section 10. Conclusions concerning cost-effectiveness are however no clearer. This arises from uncertainty about the most appropriate modelling approach, compounded by uncertainty about all model parameters.

- Section 7.4. Due to the many assumptions associated with the parameter estimates in the PenTAG model, it is important to be fully aware of the full uncertainty in the model.

2. **Clinical Effectiveness**

We believe that PenTAG have inadequately addressed clinical effectiveness. The efficacy of the AChEIs in mild to moderate AD has been well recognised by regulatory authorities worldwide, in terms of cognitive, functional, behavioural and global outcomes. These medicines have been widely used for many years. We contend that there is little new information to add to this established situation and PenTAG, by concentrating on the small amount of post-2004 data, have in effect downgraded the overall good quality of the extensive pre-2004 relevant clinical trials.

Reference to sections of the report which support Shire's view:

- In their Summary of clinical effectiveness evidence, PenTAG have concentrated on trials since 2004 and have concluded that overall the quality of the trials was

disappointing (section 4.10). Few new trials were found. This fact is not surprising, since the drugs are mature and the period for conducting registration trials has largely passed. In our opinion, it would have been preferable for PenTAG to have concentrated in their report largely on all trials of these drugs, rather than recent studies.

- Nonetheless, PenTAG commented for galantamine in section 4.10 that pooling of data from galantamine studies showed clear benefits from cognitive, functional and global outcomes. Additionally, results favouring treatment were seen for behavioural outcomes at later (six month) follow-up.

- In section 1.3.2 the report states that important gaps remain in the evidence concerning long-term outcomes, impact on quality of life, carers and time to institutionalisation. Shire has endeavoured, in their submission of June 2004 and subsequently, to provide evidence for the treatment effect of galantamine on long-term outcomes, caregiver burden and time to institutionalisation.

- In sections 1.5.1 and 9.2 the report comments that 'None of the trials conducted sub-group analyses based on disease severity, making us unable to comment on the effectiveness of treatments for mild, moderate or severe AD separately.' However, in section 4.4.2 the report correctly recognises that 'The Shire submission provided additional analyses indicating an increase in effect with increasing severity of disease.' It is correct to state that such sub-group analyses have not been performed for individual trials but it appears unfair for PenTAG to claim to be unable to comment on the effectiveness of treatments for mild, moderate or severe AD separately, given Shire's detailed analysis of mild-to-moderate AD in the submission of June 2004, repeated subsequently during the long appeals process and again in the recent 2010 submission.

- In sections 1.5.1 and 9.2 the report comments that 'Overall the quality of the trials was moderate to poor, with lack of reporting of key measures of trial quality, thus adding to the uncertainty of the results.' This statement refers to trials since 2004 and unfairly, in our opinion, does not refer to the quality of regulatory trials conducted before 2004.

- In section 1.6 the report concludes that 'The additional clinical effectiveness evidence identified in this up-date systematic review continues to suggest that there is clinical benefit from the AChEI's in alleviating symptoms and controlling disease progression in Alzheimer's disease.' This statement endorses AChEI clinical effectiveness but we believe that the evidence 'confirms' rather than 'suggests' clinical benefit of these licensed drugs.

3. Cost Effectiveness

We refer to point 1 above and in particular to items listed under 1.5.2 in the assessment report in which PenTAG itself describe limitations of their report and refer *inert alia* to limitations of the model and of associated cost-effectiveness conclusions. We add further related points below.

- In section 1.4.3 the report states ‘Despite modifications to overcome problems highlighted in the last appraisal, the results of the PenTAG model were not dissimilar to the results for the last TAR, indicating that neither AChEIs nor memantine are cost-effective irrespective of the severity of AD being considered.’ In fact the AChEIs were estimated to be cost-effective for moderate AD patients in the last TAR.

- In section 1.5.2 PenTAG state ‘In attempting to overcome a criticism of the SHTAC model where AD progression was based on US data, AD progression in the PenTAG model is based on UK individual patient data. However, the generalisability of this data should be questioned for a number of reasons: (i) the data are from just 92 individuals, (ii) it is collected from Oxfordshire only, and (iii) these data are now rather out of data, as they were collected between 1988/9 and 1999. Not only are these data used to inform AD progression, they are also used as a basis for the NHS/PSS costs of care (in the community and in institutions)’. We also question this inadequate derivation of AD progression.

- In section 1.6 (Conclusions) concerning cost-effectiveness, the report raises the question of the ‘uncertainty about the most appropriate modelling approach, compounded by uncertainty about all model parameters.’ We agree with the report’s view on model uncertainties.

We appreciate the honesty of PenTAG above in recognising the limitations of their model.

4. Summary

This report incorporates many shortcomings, as recognised by its authors (PenTAG). We therefore believe that there is little value in commenting at length on the fine detail of the report used to derive clinical and cost effectiveness of galantamine and the other AChEIs, in view of PenTAG’s lack of confidence in their own model. This report does not offer a basis for NICE to generate a valid opinion on the cost effectiveness of the AChEIs.

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