# Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111)

## Response to the Peninsula Technology Assessment Group (PenTAG), University of Exeter Technology Assessment Report (TAR) from RICE ( The Research Institute for the Care of Older People), Bath

We are grateful for the opportunity to respond to the above report for the review of TA111. We have a number of general comments about the limitations of the PenTAG report and there are a number of weaknesses in the model that they have used. We note on page 33 of the report the comment that there should be no initial presumption that the model from themselves as an independent review group is somehow more valid or reliable than others. They go on to comment that their own model has been developed in only 4 to 5 months, in theory with the expectations to address some of the identified weaknesses of the previous model and to be a single model capable of evaluating all the treatment comparators at different levels of disease severity (both the AChEIs and memantine).

At several points in the document they comment on the restricted time that they have had to develop their report and model. Whilst we accept that there have to be limits on such a report and its timeframe, the issue of drug treatment for people with Alzheimer's disease is too critical a subject (and caused so much controversy with the previous review) that it seems unacceptable to not take the appropriate time to develop the model and to evaluate the evidence.

Specifically the report comments (page 34, section 1.5.1) that the follow-up of trials was a maximum of 6 months whereas this is untrue. For example with donepezil, there are 2 trials (the Winblad et al Swedish study and Mohs et al study) both of which continued for a one year period. The Mohs trial is particularly innovative in that it looked at the loss of activities of daily living over the 12 month period in comparison with the placebo group. This data is mentioned in passing (in section 1.3.2 page 29) when it says that in 2004 the assessment group found that "donepezil improved cognitive and global outcomes with increased benefit from higher doses, in some cases this benefit was maintained over a year". Yet this has not been included in the current analysis. In addition there is a comment that there is little information about the effect of donepezil on activities of daily living, yet the Mohs study would potentially provide this.

The evaluation has only included published data and systematic reviews and has not attempted to include or find information from the companies where some of the published details may be limited. For example in section 1.3.1 on page 29 it mentions that methods of randomisation and allocation concealment were frequently not reported. This kind of negative comment is not helpful nor accurate since it would be very simple to get more detailed information by contacting either the authors of the papers or the company. The amount of information that can be included in a published paper of a clinical trial is limited; therefore it is often the case that information may not included to the level that PenTAG wish but not that the information is unavailable.

### PenTAG's understanding of Alzheimer's disease, its assessment and management

We are concerned that the group at PenTAG do not have an adequate understanding about the disease for which they are reviewing current treatment options. For example on page 44 discussing the aetiology of Alzheimer's disease they mention that "at least three genes have been identified that are associated with the rare condition of early-onset Alzheimer's disease". In fact

most cases of early-onset Alzheimer's disease are not associated with these three genes. On page 45, section 2.2.5.1, they mention that visual and auditory hallucinations occur in about 30% to 59% of suffers whereas auditory hallucinations are uncommon in Alzheimer's disease. However they do mention in this section (page 46) that the main predictors of full time institutional care are caregiver exhaustion, the degree of patient dependence and the rate of disease progression. Yet their subsequent classification of patients relies on cognition, and the economic model is based on a study which uses an inappropriate activities of daily living scale which we will comment on below. On page 47 and 48 in section 2.2.5.4 they discuss the outcome measures used in clinical trials of drugs for Alzheimer's disease and some of the shortcomings. They comment on limitations on the Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog) but this is the tool that has been recommended by the FDA for the licensing of drugs for Alzheimer's disease together with the global rating (the Clinician Interview Based Impression of Change plus caregiver input, CIBIC-plus).

On page 48 they discuss measures of functional status in clinical trials and state that the most commonly used are the Activities of Daily Living Scale (ADL) or the Instrumental Activities of Daily Living (IADL). They comment that the reliability and validity of these scales "has not been in the specific context of dementia" but that is because these scales are not usually used in dementia. Their own model uses the Barthel Index which we believe is inappropriate as a measure of activities of daily living for people with dementia; most studies actually use a specific measure, the Alzheimer's Disease Co-operative Study – Activities of Daily Living Scale (ADCS-ADL), which is used in the LASER AD study that they also quote within the economic model that they have developed. They also mention that the DEMQOL has been validated as a measure of health related quality of life in people with dementia yet in clinical trials the most frequently used measure is the patient-rated QoL scale. DEMQOL has only recently been introduced and there are a number of reservations about this scale but it has certainly not been available for use in clinical trials until very recently.

In their background document, on page 57, section 2.3.1.2 discussing memantine they mention that the UK marketing authorisation is for treatment of people with moderate to severe Alzheimer's disease (measured by the MMSE, score of 20 or less). This is in fact a change from the previous NICE assessment of memantine which only included people with an MMSE score of 15 or less. Yet it appears that their review has omitted data from 2 more recently published trials (Bakchine et al 2008, Peskind et al 2006) even though data from these trials (which looked at mild to moderate patients) were used to obtain the extension of the European licence for memantine to cover patients up to an MMSE of 20 or less. This data is readily available and should have been included, otherwise a significant amount of data which led to the extended licence for memantine has not been evaluated in this present assessment. Their information about dosing of memantine is also out of date since the current recommendation is that the starting dose should be 5mg once daily increasing to a maximum daily dose of 20mg per day (and not twice daily as stated on page 57 of the evaluation).

On page 76 the TAR comments on the Lundbeck submission and the methods used to pool data which relied on individual patient data to which PenTAG did not have access. Did PenTAG ask Lundbeck for access to this individual patient data?

They were also concerned about the pooling of data from trials of memantine alone with trials of memantine plus AChEIs. This data reflects the reality that in the United States, France and a number of other countries best practice is for the use of AChEI followed at a later stage by the addition of memantine. It also reflects the fact that data from such studies was included in both the EMEA and FDA assessment of memantine for the approval of its licence for use in moderate to severe Alzheimer's disease. On page 77, PenTAG comments that it could not repeat the Lundbeck evaluation of the sub group with Agitation / Aggression and / or Psychotic symptoms because it depends on individual patient data. Given the current concern about the inappropriate use of antipsychotic agents in people with Alzheimer's disease, this is an important issue which needs to be assessed properly. We understand that NICE did indicate that the current review would look at sub group data particularly regarding the potential of these agents as alternatives to

antipsychotic drugs. This is a particularly important issue and fails to reflect current practice where, despite the current NICE guidance, many clinicians are using memantine because it does appear to have a beneficial effect in reducing agitation and aggression and in reducing the need for the use of antipsychotic agents. Given the difficulties of these behavioural problems and that they are one of the major causes for institutionalisation of people with dementia it is a pity that this has not been adequately addressed by this review.

**Studies included in this review**

We have already commented on the exclusion of some of the one year studies with donepezil. We are also surprised that the review has not included the systematic reviews that exist for all of these compounds carried out by the Cochrane Collaboration. Instead on page 72 section 4.3.1 the report states that there are no systematic reviews of donepezil, galantamine or memantine that matched the inclusion criteria. The only Cochrane review that is included is an updated review by Birks et al (2009) of rivastigmine.

**Head-to-head comparisons**

We note the comment in section 4.7.1.3 on page 171 that the TAR considered the study by Bullock and colleagues comparing rivastigmine and donepezil (and sponsored by Novartis) to be a good quality study which although it found no significant differences between the drugs for cognitive or behavioural outcomes did note that for functional and global outcomes patients taking rivastigmine faired significantly better. However we are concerned that this review has not considered adverse events within this trial although they are noted in table 41 on page 169. Significantly more patients dropped out of the study on rivastigmine in comparison with donepezil such that the main trial data base includes 453 patients who remained on donepezil in comparison with only 404 who remained on rivastigmine. Of note is the fact that there were significant differences in the incidence of 3 adverse events between the 2 drugs, all of which were more common on rivastigmine, namely nausea 12.9% versus 5.35% donepezil, $p < 0.001$; vomiting 15.3% versus 4.4% donepezil, $p < 0.001$ and anorexia 6.4% versus 3.1% donepezil, $p = 0.031$. These are obviously important when reviewing the evaluation of such a “good quality study” to include both efficacy and tolerability in drawing conclusions about the study.

**Concerns about the use of the Oxford study (Wolstenholme et al) as the basis of the PenTAG economic model**

The Oxford study which has provided the main basis for the PenTAG model is a small study initially of 100 patients for which data on 92 is included. On page 266 of the TAR it refers to this study as the 1997/8 UK-based study yet this study in fact took place from February 1988 to August 1999. This data is therefore from a significant time ago when no specific drug treatment was available for Alzheimer’s disease until 1997 with the marketing of donepezil. The overall current management of people with Alzheimer’s disease and the awareness of the condition is quite different from the situation in the 80s and 90s. The subjects included in this study did not just have Alzheimer’s disease and it is clear from the paper (reference 181, TAR report) that around 10% of the subjects did not have Alzheimer’s disease. This inevitably dilutes the validity for using this study as the basis of the economic model. The main age of onset of the subjects in this study is estimated at 73 and this is younger than would be expected from a population in a typical memory clinic.

Although it states that the Barthel Index was used as the ADL measure, in fact this is not the case but the study actually used a different scale called the Present Behavioural Examination (PBE) which has not achieved widespread usage in dementia studies beyond its initial development in Oxford. The PBE data was transcribed to the Barthel Index and the paper states that the “transformed data were believed to have good validity” though no evidence is presented in the

paper to justify this conclusion. The Barthel Index in any case is not an appropriate measure of function in Alzheimer's disease and is never used in current dementia research nor has it been used for many years. It is a scale developed for use in stroke and physical conditions: it concentrates on measures such as walking, moving from a wheelchair to a bed, and controlling bowels and bladder. In a book from 1999 (Assessment Scales in Old Age Psychiatry, Burns A, Lawlor B, and Craig S; Dunitz 1999, ISBN1-85317-778-4) the Barthel Index is described as a scale for "assessment of physical disability in elderly people". It certainly does not adequately catch the more complex activities of daily living which would still be maintained in most patients with mild Alzheimer's disease and many with moderate Alzheimer's disease. This study is also atypical in that there are 51% male subjects whereas as commented elsewhere in the TAR, Alzheimer's disease is more common in female subjects.

We therefore have significant reservations about the appropriateness of the Oxford study as a basis for all of the PenTAG economic modelling.

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