Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111)

Dear Kate,

Many thanks for the opportunity for Novartis to review the Technology Appraisal Report (TAR) for the above appraisal. Please find overleaf a table of our detailed comments.

The TAR describes the development of a new model based on time-to-institutionalisation. The aim of this new approach is to improve on the existing SHTAC-AHEAD model which was used in the previous two NICE appraisals. Novartis recognises the substantial challenges facing the Assessment Group in developing a model of Alzheimer's disease; however, we have concerns with the new analysis and would like to raise the following key points:

1. To use this particular type of model a number of additional assumptions have been required to transform the input data into the format required to fit the model. Novartis are concerned what impact these transformations have on the final cost-effectiveness results. These transformations were not required in the previous models which were based on change in MMSE.

2. The new model is populated with patient level data from a cohort based on a small study of between 75 and 92 patients. After stratifying by disease severity this can be as few as 21 patients.

3. As well as the small size, we have doubts about the true diagnosis of some of the cohort and the overall generalisability. We believe these are substantial limitations to the dataset and so require greater analysis and discussion in the TAR if the reader is to be convinced of its suitability.

Given these shortcomings, Novartis are unclear what the specific advantage is of the new model compared to the previous SHTAC-AHEAD model. We suggest that greater evidence is needed to convince the reader why this new approach is an improvement at all. We also suggest that if greater evidence is not available then the existing SHTAC-AHEAD model should be used for the basis of this review.

We also note that the new base-case analysis significantly diverges from the analysis which the previous NICE committee based their final recommendations on. For example, carer's utility has now been omitted from the base-case analysis. This is despite the fact the NICE committee concluded it should be included. Novartis believes the base-case in this TAR should be consistent with the Final Appraisal Determination (FAD) from the previous appraisal (Sept 2009).

If you have any questions or require further information please don't hesitate to get in touch with me.

Detailed comments from Novartis on the TAR for TA111 (Aug 2010)

Clinical efficacy data		
1	Page 37 (Summary)	Here it states: "*No relevant ADL data for donepezil and no relevant MMSE data for galantamine at 21-26 weeks were identified from the clinical effectiveness review. It was assumed that this was a lack of evidence for an effect, rather than lack of effect and a class effect was assumed (i.e. the effectiveness was assumed to be the same as the other AChEIs).*" Novartis are unclear that assuming a class effect is an unbiased assumption. We believe this assumption has a detrimental impact on the analysis of rivastigmine. We note that on page 329 and Table 120 the deterministic sensitivity analyses have examined the impact of the ADL data and MMSE data on the final cost-effectiveness result. However, we are unclear if this sensitivity analysis took into account that the base-case ADL data for donepezil and the base-case MMSE data for galantamine are themselves based on an assumption of class effect. Novartis suggests that the discussion of the deterministic sensitivity analysis on page 329 needs to reflect on the initial assumption of the ADL data for donepezil and the MMSE data for galantamine.
2	Page 123, Section 4.6.3.1.	Here it discusses which rivastigmine versus placebo trials have been included in this appraisal. Novartis note that the update appears to have missed out two randomised controlled trials. We believe the following studies should be discussed in this section: **Trial B105**: Sramek JJ, et al. Safety/tolerability trial of SDZ ENA 713 in patients with probable Alzheimer's disease. Life Sciences 1996; 58: 1201-7. **Trial B351**: Spencer CM, Noble S: Rivastigmine. A review of its use in Alzheimer's disease. Drugs Aging. 1998; 13 (5): 391-411.
3	Page 131	Here it discusses the meta-analysis of the outcome MMSE for rivastigmine capsules. Page 273, Table 108, explains how this result was then incorporated into the new decision model. From this discussion it appears that for MMSE, only Feldman & Lane 2007 and Winblad 2007 have been used. There are further discussions of the MMSE meta-analysis in Appendix 5, pages 86 and 87. However, there doesn't appear to be any discussion around the MMSE endpoints from Corey-Bloom 1998 and Rösler 1999. Novartis suggests that the MMSE endpoints from Corey-Bloom 1998 and Rösler 1999 require discussion. In addition, we believe the selection and justification of which MMSE data was used in the model needs to be discussed further. Without a precise understanding of why different trials were selected as inputs for the health economics model it is difficult for the reader to confirm if the final cost-effectiveness result is based on sound evidence.
4	Page 34 and Page	Here it states: *"the length of follow up of the trials was a*

	373	*maximum of six months, which makes it very difficult to reliably extrapolate findings years ahead."* However, where it describes the approach undertaken to identify studies for the TAR it states: *"The review protocol made provision for broadening search criteria to include some observational evidence if insufficient systematic reviews or [Randomised Controlled Trials] RCTs were identified; however, this proved unnecessary in view of the reasonable yield of evidence of a preferred design."* It would appear from the general comments around the length of the available RCTs that the authors of the TAR should have considered long-term observational evidence. Novartis suggests all of the observational studies are reviewed as a source of longer term data.
Resource Cost data		
5	Cost of rivastigmine capsule Page 300, Table 113	Here it describes the drug costs used in the model. For rivastigmine capsules (9-12mg/day) the calculation of daily cost is: *"Calculated as a weighted average of daily costs for 9mg (0.7*£3.56) and 12mg (0.3*£2.37), leading to daily drug cost of £3.21"* The reference for the cost is BNF 58 to derive the Sept 2009 cost. Novartis would like to highlight that in BNF 58 the cost of the 4.5mg capsule was £33.25 for 28 or £66.51 for 56. Taking either pack size this gives a cost per tablet of £1.19 Taken as 2 x 4.5mg to give a daily dose of 9mg this results in a cost per day of 2 x £1.19 = **£2.38** We believe the daily cost of £3.56 which has been calculated in the TAR assumed the patient would take 3 x 3mg tablets a day. In our opinion this is illogical and an unnecessary pill burden on the patient. From our perspective this is also not part of the recommended dose titration detailed in the Summary of Product characteristics (SmPC) for Exelon capsules. The cost of the 6mg capsule in the TAR is correct. Novartis believes this miscalculation of the cost of the 9mg dose will have a substantial impact on the cost-effectiveness of rivastigmine capsule compared to the other therapies.
6	Page 352	We note that the new model has smaller institutional costs compared to the previous SHTAC model in the 2004 appraisal. This is due to the shorter estimated survival time in the new model of 3.8 years compared to 5.6 years in the SHTAC model. The cost of institutional care has a major impact on the cost-effectiveness of the therapies and Novartis believes this further highlights the divergence of the two models. At present it is

		difficult for the reader to understand why the new model should be considered the more robust analysis and so suggests that a greater level of discussion is needed to convince the reader the new model is the more appropriate analysis.
7	Table 120, page 329	In the previous 2004 NICE appraisal the sensitivity analysis explored the scenario of 100% of the cost of institutionalisation being funded by the NHS/PSS. Novartis note that the maximum percentage considered in the TAR is 90.6% and suggest that the maximum should be 100% to allow comparison of the results with the previous appraisal.
8	Page 299	Pages 47 and 50 discuss that the provision of care for people with Alzheimer's disease is shared between informal voluntary care, private care, Social Services and the NHS. Novartis are aware that the current NICE base-case excludes non-NHS and non-PSS costs. However, this is a NICE policy decision and we feel it would be of interest to explore what effect a change in NICE's policy would have. We therefore, suggest that the sensitivity analysis should explore this and include a scenario where informal carer's costs are included.
Quality of life / utility data		
9	Page 276	Here it states: *"A consequence of using the UK dataset from Wolstenholme is that functional capacity is measured on the Barthel ADL index, an index not used or reported in any of the included RCTs. To incorporate this information the effectiveness evidence from the ADCS-ADL scale used in the RCTs had to be translated onto the Barthel ADL index."* Firstly this succinctly highlights the shortcomings of using the Wolstenholme cohort as the basis of the model and raises questions as to its suitability over the previous modelling approach. Secondly, Novartis are unclear what is the basis of the estimated quadratic mapping of ADCS-ADL used in trials to Barthal ADL used in the UK cohort. Novartis would like to highlight that this is a substantial change to the way utility was handled in the 2004 appraisal and suggest a greater analysis of the implications of this are added to the TAR. In addition, we note that this mapping is based on the US study Galasko et al. 2005. On page 262 of the TAR it explains that part of the rationale for developing the new model was due to "*The reliance on the US data had been identified as one of the more important perceived limitations of the previous modelling."* Novartis suggests the implication of using US data in the mapping of utility is fully explored in the discussion and that the TAR maintains a consistent approach to using non-UK data in the economic modelling.
10	Page 297, Table	This reports the utility by MMSE stratification. Novartis would like

	111	to highlight that Winblad 2007 which compares rivastigmine capsule with rivastigmine patch has shown that the patch formulation is associated with markedly reduced gastrointestinal side effects compared with rivastigmine capsules. In addition, it showed the rates of nausea and vomiting with the rivastigmine 10cm^2 patch were not significantly different to those of the placebo group. It is not clear to Novartis if the utility score used in the model has taken into account the reduced side effects seen with the patch formulation compared to capsules. We suggest this is further explored in the TAR.
11	7.3.9.2. Quality of life of the carer Page 330	In the previous NICE appraisal the Final Advice Determination (FAD) (Sept 2009) concludes in section 4.3.10.3 that *"...the incorporation of carer benefits in the economic modelling in the form of utilities was appropriate"*. Novartis are extremely surprised that in this TAR the base-case analysis now excludes carer utility. We are unclear why the authors have decided to do this. We suggest that the base-case should be consistent with the previous work and carer utility should be included.
12	7.3.9.2. Quality of life of the carer Page 298	In the sensitivity analysis quality of life of the carer is incorporated into the model. However, due to the type of model the utility of the carer could not be applied directly. CDR stages were firstly mapped to MMSE and then this was subsequently mapped to time to institutionalisation. This serial mapping is described on page 298, and Novartis believes this is complex and far from transparent. It's also worth noting that the original source of the utility identified in the TAR is Neumann 1999 who themselves conclude that they are unsure if the tool they used (HUI:2) to determine carer utility was subtle enough. This discussion is reiterated in the 2009 FAD and is part of the reasoning why in the previous NICE appraisal carer utility was further explored. Novartis suggests that the TAR needs to explain clearly the magnitude and effect of carer's utility in this new analysis compared to the analysis discussed in the 2009 FAD. This will then enable the reader to understand if carer utility is being applied consistently with the previous FAD or not.
Model cohort		
13	Section 7.3.3., Page 266	Novartis believes the cohort used to populate the new economic model (further described in Wolstenholme 2002) has a number of short comings which could affect generalisability: Firstly, the sample size of 92 patients of which 82 were dead before the 11 year follow up is small when compared to the thousands of patients who have been enrolled in randomised clinical trials. At 3 years 60 patients in the study were still alive; at 6 years and 9 years only 16 and 10 patients were still alive, respectively. (See Figure 1, Wolstenholme 2002). In summary, this is a mean follow up time of only 40 months (or 3 years and 4 months).

14		Secondly, there is some confusion over the diagnosis of the population and many of the 92 patients may not have had Alzheimer's disease. In the TAR it states: "This data represents a prevalent cohort of 92 patients with Alzheimer's disease." However, in Wolstenholme 2002 it describes an overall population of 100 patients of mixed dementia population. Of which: <u>By pathological diagnosis</u> 51 Alzheimer's disease, 6 Alzheimer's disease/vascular dementia 2 vascular dementia <u>By clinical diagnosis</u> 28 Alzheimer's disease 7 Alzheimer's disease/vascular dementia 1 vascular dementia 5 other types of dementia This makes a total of 51+28= 79 individuals diagnosed with Alzheimer's compared to the 92 which the TAR describes. Furthermore, Wolstenholme 2002 details that the cohort data was taken from an observational study conducted by Hope (*Hope et al, 1997. International Journal of Geriatric Psychiatry, 12, 1062-1073*). In this reference it describes a population of only 75 patients with Alzheimer's, composed of 28 with probable Alzheimer's and 47 with definite Alzheimer's. In light of this uncertainly, Novartis suggests that Section 7.3.3 of the TAR needs to clarify exactly how many patients used in the model cohort actually had Alzheimer's.
15		It's also worth noting that the cohort data was collected between 1988 and 1999 which means the most recent recording was 11 years ago. This may mean the resource use may no longer represent current UK practice. In addition, the population is restricted to Oxfordshire so may not be representative of the rest of the UK.
16		The cohort also has a mean time since diagnosis of 4.9 years. However, further details of the distribution of time since diagnosis is not discussed. There are also no further details in the reference for the cohort (Wolstenholme 2002). The final scope for this appraisal (November 2009) states the appraisal is for adults with Alzheimer's disease. Novartis suggests that more discussion is added to the TAR to explore whether the cohort used in the new decision model reflects the NICE scope or not.
17		Novartis also note that patients in the new model cohort were older with worse cognition at the point of entry, as compared to the previous SHTAC model in the 2004 appraisal.

		Since the patient population in the latest model was Alzheimer's and mixed dementia, notably vascular dementia, it is unclear if the shorter estimated survival time is an accurate reflection of Alzheimer's progression. This again raises doubt as to how representative the new model is of the cost-effectiveness of therapies for the treatment of Alzheimer's.
18		It appears that no data on psychotropic drug use was collected for the cohort. Novartis believes it is important to consider this when studying behaviour in Alzheimer's patients. We believe the use of psychotropic drugs could impact behaviours that might influence MMSE or Barthel Index, and the associated time to institutionalization. Time to institutionalization is the key driver of the outcome of the new model and so any uncertainty in this variable needs to be discussed. Novartis suggests that this uncertainty is explicitly stated in the TAR and the sensitivity analysis needs to explore its impact.
19		Finally, the cohort is an observational dataset. As highlighted in our earlier comment (number 4), the authors of the TAR decided to exclude all other observational datasets. It's worth considering this decision in light of the comments on page 266 which state: *"A UK-based epidemiological cohort study, such as that by Wolstenholme and colleagues was preferred over clinical trial data to avoid any biases of assuming disease progression based on RCT populations which are subject to a number of inclusion and exclusion criteria not representative of our target population: people with Alzheimer's disease in England and Wales."* Further reading of Wolstenholme 2002/Hope 1997 reveals that the cohort also had inclusion/exclusion criteria. For example excluding subjects who drank more than 30 units of alcohol per week for more than 2 years at some stage in their lives, and excluding those patients in whom the carer was not able to give an accurate account of the day-to-day behaviour of the subject. Novartis suggests that a consistent approach to open label studies is maintained throughout the TAR.
Presentation of analysis		
20	Figure 75 (Page 319), Figure 76 (Page 320, and Figure 88 (Page 338)	These are cost-effectiveness planes. However, in none of these figures best supportive care is not at the origin. This implies that another treatment is at the origin. Novartis are unclear what this treatment is. So we suggest that the TAR makes it clear what therapy is at the origin in the three figures and explains what is being compared in the figures.
Typographical errors		
21	Page 124, Table 17	In the fourth column 'Methodological notes' it states: "Plus ratings of .4 of 20% within the BID rivastigmine group (35% rivastigmine vs 15% placebo)." Novartis believe there is a minor typo and it should state: "Plus ratings of **>**4 of 20% within the BID rivastigmine group (35% rivastigmine vs 15% placebo)."

22	Page 126, Table 18	In the 11th column 'Duration of dementia (mo)', first line, it states the standard deviation is "25.5". We believe this should be "24.5".
23	Page 126, Table 18,	In the third column, finial line, it states the dose is 4.75mg/d. We believe this should be 4.6mg/d.
24	Page 127, Table 18,	Here is summarises the additional rivastigmine studies that have been identified. In the Winbald line (Rivastigmine patch -20cm^2) the number of patients (N) is 303 instead of the stated 302, and the percentage of white patients should be 74.9%.
25	Page 130, Table 20	In the seventh column, Winblad et al. 2007 row, Ten-point clock-drawing test – 24wk outcome, the 10cm^2 and 20cm^2 results are the wrong way round. The 10cm^2 number of patients should be 245, the mean should be 0.3, and the SD should be 3.4. For 20cm^2, the number of patients should be 251, the mean should be 0.1, and the SD 3.1.
26	Page 133, Table 21	The first row, Feldman & Lane 2007 results, the bd and tid appear to be the wrong way round.
27	Page 137, Table 23	The first row, Feldman & Lane 2007 results, again the bd and tid appear to be the wrong way round.
28	Page143, Figure 42	In the final line, Winbald 2007 the number of patients (N) is 303 instead of the stated 302.
29	Pages 30, 74, 139, 142, 190, and 367	In several places in the TAR it refers to the 9.5mg/day rivastigmine patch as the lower dose transdermal patch. Novartis would like to highlight that in the BNF it lists two rivastigmine transdermal patches: 4.6 mg/24 hours and 9.5 mg/24 hours. Novartis suggests to avoid confusion to the reader that the 9.5 mg/24 hour patch is not referred to as the lower dose patch in the TAR since this is the highest licensed dose in the UK.
30	Page 33	We also note that the 9.5mg/day rivastigmine patch is sometimes referred to as the 10cm^2 patch in the TAR. Novartis appreciates that this is how the dose is described in some publications, however we suggest that in the summary on page 33 of the TAR it is made clear that the 10cm^2 patch is describing the 9.5mg/day dose.