

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease

### Appeal by the Royal College of Psychiatrists and the British Geriatrics Society

#### Decision of the Appeal Panel

#### 1. Introduction

- 1.1. The Appeal panel convened a hearing on 13 and 14 July 2006 to consider an appeal against the Institute's Guidance to the NHS on the use of donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease, as set out in the Final Appraisal Determination produced by the Appraisal Committee ("**the FAD**").
- 1.2. The Appeal Panel comprised Dr Susanna Lawrence (Chair of the Appeal Panel and Vice Chairman of the Institute's Board), Mr Frederick George (non-executive member of the Institute's Board), Ms Jean Gaffin (Patient Representative), Mr Roy Luff (non-executive member of the Institute's Board) and Professor Peter Stonier (Industry Representative).
- 1.3. The appeal was lodged by the following appellants: the Royal College of Psychiatrists and the British Geriatrics Society.
- 1.4. The following individuals involved in the appraisal were present to answer questions from the Appeal Panel: Professor Andrew Stevens (Chair), Dr. Carole Longson (Director, Centre for Health Technology Evaluation), Mr Andrew Dillon ( Chief Executive, National Institute for Health and Clinical Excellence), Mr. Meindert Boysen ( Technical Lead, National Institute for Health and Clinical Excellence), Alec Miners ( ex- Technical Lead), Dr Karl Claxton ( Committee Member), Dr John Geddes ( Committee Member) and Mr Julian Gizzi ( legal representative)
- 1.5. The three grounds on which the Appeal Panel can hear an appeal are:

- (1) The Institute has failed to act fairly and in accordance with its procedures;
  - (2) The Institute has prepared guidance which is perverse in the light of the evidence submitted; and
  - (3) The Institute has exceeded its powers.
- 1.6. Over the course of the two day hearing, the Panel heard a large volume of information regarding Alzheimer's disease, the technologies under appraisal, the lengthy process that had taken place since the scope for the appraisal was first identified in January 2004 and the deliberations of the Committee in reaching their conclusions.
- 1.7. The Panel were aware of the devastating nature of Alzheimer's Disease, and the severe distress and difficulty caused to patients, carers, and family members. They were informed of the specific nature of the technologies, namely that some treatment benefit for some patients was established, but that this was small and time limited, and served to ameliorate the symptoms of the disease rather than prevent deterioration.
- 1.8. They recognised the dilemma facing the Appraisal Committee, in that they were charged with assessing the costs and benefits of a wide range of technologies across the whole disease spectrum, affecting the population as a whole. The Appeal Panel understood that the Committee had to be fair to the entire population in assessing cost effectiveness. They were advised that, in relation to other technologies, the cost of treating all patients with Alzheimer's disease was great, given the limited clinical benefit, and that they were unable to recommend the technologies for all patients for this reason. The Panel recognised the efforts of the Appraisal Committee in attempting to identify the groups of patients who would respond best to treatment. The Panel heard that the Committee had been able to identify a group of patients with Alzheimer's disease who would achieve most benefit from the treatment, and that the FAD recommended treatment for this group, namely people with moderate and moderately severe disease. The Panel recognised that this was an important development from the earlier draft guidance, where the cost/benefit ratio had precluded recommending treatment for ANY people with Alzheimer's disease.
- 1.9. The Panel heard the view of the Appraisal Committee, reflected in the FAD, that targeting treatment for people with moderate disease would result in about 40% of people with Alzheimer's disease being eligible for treatment. In the earlier guidance, where initial responders were the subgroup targeted for treatment, the projected figure was also 40% of

people with Alzheimer's disease. The Appraisal Committee judged that the current FAD better identified the patients likely to receive most benefit from the treatment.

## 2. Ground 1

### **1. The institute failed to consider the wider merits, particularly when there are considerable uncertainties regarding the robustness of the health economic data.**

- 2.1. The Appeal Panel questioned the Appraisal Committee Chairman regarding the use of QALYs (Quality-Adjusted Life Years). Whilst stating that QALYs were used in order to provide a common outcome measure to allow comparisons of cost effectiveness to be made across all morbidities, he accepted that QALYs were particularly difficult to measure in this patient group. Because of this difficulty, the Committee had not relied solely on the Assessment Group's analysis, but had tested the data using the EQ-5D health state tariff methodology, the cost utility analysis used in the augmented base case described in Technical Report 1, and the LASER-AD (Livingstone et al 2004).
- 2.2. The Panel heard that the Committee had used figures, reflecting a more optimistic interpretation of the data in relation to the transition from pre full time care to full time care, in order to accommodate remaining doubts regarding the estimates.
- 2.3. Furthermore, the Panel heard that the final reworkings produced results very close to those in the three industry submissions.
- 2.4. The appellant asserted that the use of QALYs produced further unfairness to the patient group as they tended to discriminate against older populations. The Panel noted that this was only the case for technologies where an extension of life was part of the clinical picture, and this was not the case for the antimentia drugs.
- 2.5. The Committee recognised the wide range of cost/QALY estimates, but explained that with several different parameters this would be expected. They did not believe this range was particularly wide when compared to other technologies.
- 2.6. The Panel concluded that, although there was a degree of uncertainty concerning the QALY calculations, the Committee had reduced the risk of that uncertainty as far as possible through testing and upward adjustment.

- 2.7. However, the appellants' assertion was also that, given the uncertainties regarding QALYs, the wider merits of the technology had not been taken into account.
- 2.8. The Panel questioned the Committee regarding the particular needs of the patient group. Whilst the Committee had fully recognised that the effects of Alzheimer's disease were devastating to patients and carers, they were mindful that their role was to examine the technologies, and ensure that in evaluating their clinical and cost-effectiveness they were fair to all patients using the NHS.
- 2.9. Regarding the innovative nature of the technology, the Committee confirmed that they had considered the fact that the technologies in question were the only pharmacological intervention available for this patient group. The Panel noted that the use of QALYs tends to work to the technology's advantage when there is no comparator.
- 2.10. The Panel heard the concerns of the appellants regarding the possibility of threat to awareness and services for people with Alzheimer's disease. They questioned the Committee members as to whether they had considered this possible consequence of Guidance arising from the FAD, and were satisfied that they had, but had concluded that any consequences were speculative and as such did not change the guidance given in the FAD.
- 2.11. The Panel questioned the Committee members regarding the changes in recommendations from the previous Guidance TA19. The Panel were advised that the clinical evidence base had grown, with increased numbers of trials for all the acetylcholinesterase inhibitors. This new data strengthened the degree of certainty over the benefits of the technologies, but indicated that the earlier optimism regarding the potential size of the benefit had not been realised.
- 2.12. The Panel also heard that the methodological expertise in analysing cost-effectiveness data had improved since TA19, so although there was no new cost effectiveness data, there was much greater expertise available to interpret the data.
- 2.13. The Panel noted that although a different group of patients were targeted, both TA19 and the guidance proposed in the FAD resulted in the treatment of approximately 40% of patients with Alzheimers Disease.
- 2.14. The Panel considered all the above points and concluded that the Appraisal Committee had recognised the limitations of QALYs, had sought to address them and had considered the wider merits of the technologies.
- 2.15. Appeal Point 1 was therefore dismissed.

2.16. Under Ground 1, the Panel considered the related additional ground originally brought under Ground 2 (point 4 in the appeal letter):

**The reliance placed on QALYs derived from Neumann's Health Utilities Index<sup>2</sup> as the sole basis for assessing cost-effectiveness in Alzheimer's disease is severely flawed.**

2.17. The Appeal Panel asked why the Committee had used a scale not evaluated in dementia, and reliant on proxy measures, and were informed that it was the best available, and that the measures described previously (testing and upward adjustment) sought to address these concerns. The Committee members confirmed that the alternative methods cited by the appellant had all been included in their deliberations.

2.18. The Panel were satisfied that the Committee had looked fairly at all the evidence.

2.19. This additional point was therefore dismissed.

**2. The Appraisal committee chose to apply a very small QOL gain to carers. It is not clear what evidence base this estimate came from.**

2.20. The Committee had taken evidence from carers at the ACD meeting, and members of the Guideline Development Group were present at all Committee meetings.

2.21. The Panel heard that costs for informal carers are not normally included in assessing a technology's cost-effectiveness, but it was in recognition of the particular and important role that carers play in the care of people with dementia that a carer utility was included in the analysis for this technology.

2.22. The Appeal Panel heard that the Appraisal Committee was mindful of the need to avoid 'double counting', and therefore needed to use either carer time or QOL gain as a measure of the effect on carers of the technology. As their brief was to develop guidance that took account of PSS/NHS costs, they used the index most able to be converted into monetary terms, namely QOL gain.

2.23. For this reason, references to carer time saved had been removed in the FAD. It was pointed out that in paragraph 4.1.3.7 there was reference to carer time saved with galantamine treatment. The Appraisal Committee stated that, in the interests of fairness, this reference should be removed from the FAD.

2.24. The Panel heard that the studies considered showed no difference in carer quality of life across the disease spectrum. In other words, the impact of the disease on the carer was similar whether the patient had mild, moderate or severe disease. As explained in Technical Report 1, the augmented base case contained a utility loss of 0.01(from Neumann, 1999) from the beginning of care until the person they cared for required full time care. This was the best possible interpretation of the data regarding the change in impact on carer QOL that could be brought about by using the technology.

2.25. The Panel were satisfied that the Committee had made considerable effort to identify carer benefits of the technologies, and had included a factor that was optimistic given the data. They concluded that the Committee had been fair in this respect.

2.26. The Appeal Panel believed that there was merit in the suggestion from the Chairman of the Appraisal Committee to omit references to carer time in paragraph 4.1.3.7, and accordingly refer this point to the Guidance Executive.

2.27. In other respects Appeal point 2 was dismissed.

### **3. No significant weight has been given to the unanimous views of patient, carer, and professional organisations.**

2.28. The Appeal Panel were satisfied that the Committee had both consulted and heeded the advice of patients, carers and professional organisations, as is clearly indicated in paragraphs 4.3.1, 4.3.9, and 4.3.10 of the FAD. The Panel appreciated that the Committee had acknowledged the particular role of informal carers for this patient group in including carer benefits within the augmented base case.

2.29. Appeal Point 3 was therefore dismissed.

### **4. Over-reliance on MMSE scores is both inappropriate and discriminatory as the MMSE is heavily influenced by factors such as age, sex, education, ethnicity and linguistic abilities.**

2.30. The Appeal Panel questioned the Appraisal Committee Chairman as to why the Committee had chosen MMSE scores for defining the mild, moderate and severe subgroups. They heard that MMSE had been chosen because it linked evidence to practice. In trials, both ADAScog and MMSE had been used extensively in measuring primary outcomes, but ADAScog was not practical to use in a clinical setting. MMSE was the only system that met both criteria. Furthermore, the MMSE was recommended for use in TA 19, and was accepted by all parties in that instance.

2.31. The MMSE score was the best tool available to define the subgroups, and the alternative was not to define the subgroups at all, rendering the technology cost-ineffective for all people with Alzheimer's disease.

2.32. However, the Appraisal Committee had recognised the limitations of the MMSE (paragraph 4.3.13 in the FAD): it is a screening tool and was difficult to apply for certain groups, including people with learning difficulties, people whose first language is not English, and people with a particularly high IQ. The Appraisal Committee had heard from their clinical members of the importance flexibility in interpreting MMSE scores.

2.33. People with learning disabilities were excluded from the evidence base, and therefore specific recommendations were not made for this group. The intention of the Committee was to recommend that learning disability specialists should use their judgment in interpreting or applying MMSE scores (paragraph 4.3.13). It was the express intention of the Committee that people with learning disabilities were treated differently from the population as a whole.

2.34. Regarding people whose first language was not English, the Committee agreed that clinical judgment and 'common sense' should be exercised in applying the Guidance. Like all other guidance issued by NICE, this guidance was not binding, and application had to be in the context of the whole range of clinical and social issues affecting each patient.

2.35. People with high IQ were included within the validation of the MMSE index, since trials were based on an average taken from the whole range of the population.

2.36. The Committee had deliberated as to whether to soften the subgroup thresholds by including words such as 'normally', 'usually' but concluded that the guidance would not benefit from lack of precision. The Committee had noted that under the current guidance (TA19), which had used such terminology, audit showed that approximately 70% of people with Alzheimer's disease were prescribed the technologies, whilst the evidence base suggested the responder group was likely to be around 40%. They had concluded that the 'softened' wording of that guidance had led to a failure to apply it rigorously and consequent systematic use of the technologies outside the guidance.

2.37. The Committee concluded it was more appropriate to maintain precise guidance, whilst dropping the lower end of the moderate subgroup from 12 to 10 in order to accommodate the necessary flexibility required in a clinical setting.

2.38. This point was raised under Grounds 1, 2 and 3, and so the Appeal Panel deliberated accordingly.

2.39. The Panel considered that the Committee had been fair in defining subgroups, using the best tool available, and indeed in so doing had identified the subgroup able to benefit most from the technology, thus bringing the technology within acceptable cost effectiveness limits which would otherwise not have been possible. They concluded that the Committee had not acted perversely in either their deliberations or their conclusions, given that the guidance stated, as all NICE guidance, that in individual cases clinical judgement may override guidance.

2.40. As to the specific allegation that the reliance on the MMSE was discriminatory, the Panel noted that no evidence as to the nature and extent of any such alleged discriminatory effect was advanced by the appellants. Nonetheless, it was accepted by the Committee that use of the MMSE alone might disadvantage certain individuals. Any discriminatory effect would be indirect rather than direct in nature. The Panel concluded that the guidance would not have a significant discriminatory impact if it was applied responsibly by practitioners. In the case of individuals with learning difficulties, the FAD provides in terms at paragraph 4.3.13 that learning disability patients should have their treatment initiated by learning disability specialists. The Chairman of the Committee confirmed that it was intended that a greater degree of discretion should be applied in relation to such individuals. As to other groups who might be disadvantaged, the Panel considered that the guidance permitted practitioners to apply common sense in initiating and terminating treatment, bearing in mind that clinical judgment is not overridden by the guidance. Only if the guidance were to be applied slavishly (which it should not be) would it be likely to have any discriminatory impact. Further, to the extent that any residual discriminatory impact might arise from the guidance, the Panel considered that any such outcome would be justified. It is necessary to have guidance which is reasonably clear and practical. The use of MMSE scores achieves this important objective. No alternative method of defining the subgroup, which would be totally free of any kind of potential differential impact, was put forward.

2.41. Under Ground 1, the Appeal Panel considered that the final sentence in 4.3.13 could be better worded more accurately to reflect the intention of the Committee, and referred this point to the Guidance Executive for consideration.

2.42. Appeal point 4 was dismissed under Grounds 2 and 3.

### **3. Ground 2**

**1. It is entirely perverse, and totally contrary to the view of patient, carer and professional organisations, to withhold effective therapy until the later stages of a neurodegenerative disorder.**

3.1. The Panel questioned the Appraisal Committee members regarding the differential benefits in the mild and moderate group, and heard that, although there was a statistically significant improvement in both the mild and the moderate group, the subgroup analysis demonstrated a greater magnitude response in the moderate group, as outlined in points 4.1.2.12, 4.1.3.10, and 4.1.4.11 of the FAD. There was no evidence that treating patients with mild symptoms achieved greater benefit, although the Committee acknowledged that they had heard anecdotally that improvement in the mild phase of the disease was more meaningful. The Committee did not accept that the benefit in the moderate group was a phenomenon created by the non-linearity of the MMSE with the course of the disease. Patient welfare, or quality of life, as measured by utilities, did have a linear relationship with MMSE (or ADAScog), as described in Technical Report 1.

3.2. The Committee agreed that the drugs are clinically effective at the mild stages, but were less so, thus generating a higher cost/QALY. The Committee had a responsibility to consider the wider benefits and costs of NHS resources, and considered that the cost effectiveness of the treatment for people with mild symptoms would be an unfair use of NHS resources.

3.3. The Panel ascertained that differentiation of the subgroups defined as mild, moderate, and moderately severe reflected clinical practice and was possible to implement.

3.4. The Panel formed the view that, in identifying the moderate and moderately severe subgroups as the groups that would benefit most from the technologies, the Committee had ensured that the technology was targeted most effectively, and at the same time delivered acceptable cost effectiveness.

**2. The FAD has not properly considered the issue of improving the cost-effectiveness of antideementia drugs by maintaining good responders on treatment.**

3.5. The Panel questioned the Committee members as to why they had not recommended initial responders as the desired subgroup, particularly since this was the group targeted for treatment in TA19. The Committee had rejected responders as the target treatment group because they were difficult to identify clinically (both those treated and those on placebo had apparent cognition gains at six months, and amongst the 'non-responders', those on the drug benefited relative to 'non-responders' on treatment). Further, like

any post hoc analysis, the responder analysis was difficult to interpret owing to selection bias. Regression to the mean and the inclusion of those (non-responders) with slowly progressing disease made identification of the responder group difficult. They concluded that this level of uncertainty precluded initial responders from being the appropriate subgroup to treat.

3.6. The Panel also heard that, although the evidence suggested that 40% of people with Alzheimer's disease were responders, audit performed in the NHS suggested that 70% of people with Alzheimer's disease were treated. This supported the assertion that the group was difficult to identify clinically.

3.7. The Panel heard that the Committee had deliberated between the two possible subgroups for treatment, and had concluded that treating 'responders' (as defined in TA19) was less likely to target those who would benefit most, and more likely to treat greater numbers of people who would not benefit from treatment.

3.8. The appellants asserted that the Appraisal Committee have consistently refused to consider the approach of treating mild responders. The Panel were persuaded, by hearing the response of the Committee members to questioning, as outlined above, and by the reasoning outlined in 4.3.10.7 of the FAD, that the Committee had in fact carefully considered the approach, but had rejected it.

3.9. The Panel concluded that the Committee had not reached a perverse conclusion in rejecting initial responders as an appropriate group to target for treatment.

3.10. This appeal point was therefore dismissed.

**3. The FAD would lead to later referral and later intervention, with the promotion of a nihilistic attitude that dementia would not be worth recognising or referring until subjects had deteriorated to MMSE<20.**

3.11. The Appeal Panel heard that the Committee had received comments regarding the improved package of care for people with dementia as a result of TA19 (4.3.5 in the FAD). On questioning, the Committee members were in full agreement with the appellant that the continuation of memory clinics and other interventions was paramount in offering care to people with Alzheimer's disease. A Guideline Development Group was currently in the process of writing the Guideline for managing people with dementia, and would be defining the packages of care.

3.12. The Appeal Panel decided that any negative effect on referral patterns was speculative, and it was just as likely that referral would continue

as now, as most clinicians recognised that any pharmacological intervention was only part of the package of care delivered by specialist services.

3.13. The Panel considered that the Guidance was not perverse in this respect.

3.14. Appeal point 3 was therefore dismissed.

#### **4. The reliance placed on QALYs as the sole basis for assessing cost-effectiveness in Alzheimer's Disease is severely flawed.**

3.15. This point was considered under Ground 1. However, in their deliberations, the Appeal Panel also considered the point under Ground 2. The Panel did not agree with the assertion that the Committee had relied solely on QALYs in assessing cost effectiveness. Rather, the Panel considered that the Committee had gone to considerable lengths to address the uncertainties pertaining to QALYs, in commissioning the NICE secretariat to use alternative variables in arriving at cost estimates, and in establishing their impact. The panel concluded that the Committee had not acted perversely, and had in fact worked hard to establish the most optimistic measures of cost effectiveness.

3.16. Appeal point 4 was therefore dismissed.

#### **5. The approach taken in is inconsistent and contradictory when compared with the previous 2001 appraisal, when problems with use of QALYs in AD were acknowledged.**

#### **6. No new research has become available.**

3.17. The Panel noted that the Appraisal Committee were not obliged to agree with the findings of a previous Committee, even if the same evidence were placed before them. However, in this case, there had been an increase in the size of the evidence base: the number of trials included in assessing clinical effectiveness had doubled, and whilst there was no new trial data regarding cost-effectiveness, the methodology had improved significantly since TA19.

3.18. Furthermore, the appellants were quoting from the Assessment Report, not the Guidance TA19, in citing problems acknowledged with QALYs.

3.19. The Panel were satisfied that there were sound reasons for the Committee to make different recommendations to that of TA19.

3.20. Appeal points 5 and 6 were therefore dismissed.

## **7. Non-availability of antidementia drugs will result in increased prescription of typical and atypical antipsychotic drugs.**

3.21. The Appeal Panel questioned the Appraisal Committee as to whether they had considered this possible effect of the guidance in its present form. The Chairman confirmed that it was not the intention of the FAD to result in an increased use of antipsychotics, and that the Committee had been aware that neuroleptics were not necessarily effective for agitation in this patient group. Furthermore, if antipsychotics were inappropriately prescribed for people with dementia, addressing the problem via other routes, principally the Guideline Development Group, were more appropriate. It was not desirable to write guidance to address secondary poor clinical management.

3.22. The Appeal Panel also heard that the evidence base for memantine was equivocal, and that, taken in its entirety, the clinical and patient experts who gave evidence to the committee were not particularly enthusiastic about the use of memantine.

3.23. The Appeal Panel accepted that the Committee had not acted perversely in this respect.

3.24. Appeal point 7 was therefore dismissed.

## **4. Ground 3**

### **8. The FAD requires the withdrawal of medication when people decline to a MMSE score of 10.**

4.1. The Appeal Panel noted that in paragraph 1.1 the FAD states "The drug should only be continued while the patient's MMSE score remains at or above 10 points....". The Panel considered this statement to be referring to patients with moderate disease, and therefore in line with the licensed indications. In effect, the Committee is recommending withdrawal of the drug if the patient moves outside the disease state for which the licence is granted. The Panel considered this to be entirely appropriate, and within the powers granted the Institute.

4.2. Appeal point 8 was therefore dismissed.

### **9. The FAD will *de facto* lead to severe inequities and unduly penalise a particularly vulnerable group in society.**

4.3. The Appeal Panel were aware that the likely consequence of issuing any guidance that restricted the availability of a technology was to increase the private prescribing of that technology. In this case, they considered that the Appraisal Committee had given careful thought to the clinical and cost effectiveness of the technology, the need to take into account the broad clinical priorities of the Secretary of State and the National Assembly for Wales, and wider NHS costs, and that the decision to recommend selected use of the technology in the NHS was neither perverse, nor caused the Institute to exceed its powers.

4.4. Appeal point 9 was therefore dismissed.

**5. Conclusion and effect of the Appeal Panel's decision**

6. Subject to the points referred to the Guidance Executive for consideration, the Appeal Panel has dismissed the appeal on all points.

7. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel and the Institute's decision to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision or the issuing of the Guidance.