

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Appeal by Eisai Limited

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 appellant: Eisai Limited.
- 1.4. The following individuals involved in the appraisal were present to answer questions from the Appeal Panel: Professor Andrew Stevens (Appraisals Committee 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

2.1. Before making their initial presentation, Eisai notified the Panel that they wished to raise a point regarding fairness of process. They believed that ten minutes to present the salient features of their appeal was unreasonably short, and that they should be able to present each point as they were considered. They were advised by the Chair of the Appeal Panel that they had been free to submit as much information as they wished in writing, and that it was unnecessary to repeat orally the points made in their written submission. Given the opportunity permitted to appellants to submit detailed written representations, and to raise questions and specific points during the course of the hearing, the Appeal Panel did not consider that the appellant's allegation of unfairness had any merit.

3.1 A determination that bases Guidance on a cost per QALY is unfair.

2.2. 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 study (Livingstone et al 2004).

2.3. Although the appellant disagreed with the manner in which EQ5D was used as a cross check, the Appeal Panel noted that this was not the only check performed on the model by the Appraisal Committee.

2.4. The Panel heard that the Committee had used higher 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.

2.5. Furthermore, the Panel heard that the final reworkings produced results very close to those in the three industry submissions.

- 2.6. The Chairman of the Appraisal Committee acknowledged that modelling around the two health states (pre full term care and full term care) was difficult, and that the AHEAD model used by SHTAC in the Assessment Report was the best available. The Panel also noted that the AHEAD model was used by one of the manufacturers. In recognition of the imperfections of the model, the Committee had repopulated the model with alternative data so as to provide a more optimistic scenario. They had directed the NICE secretariat to explore the model in a variety of different ways (see FAD paragraph 4.2.6.1) in order to ascertain whether more optimistic cost estimates could be assumed. As outlined in Technical Report 1, the AHEAD model and the donepezil model were reconciled using an amended starting utility of 0.69 instead of 0.6 for the pre full time health state.
- 2.7. The appellant raised the difficulty in measuring health related quality of life in people with Alzheimer's disease, and in particular the use of data derived from the Health Utilities Index 2 (HUI 2, Neumann et al 1999 and 2000). The Appeal Panel ascertained that the Assessment Group model assumed a distribution around both health states, thus incorporating a factor of uncertainty in recognition of the difficulties in measuring QOL utilities.
- 2.8. 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.
- 2.9. The Panel questioned the Committee members regarding the changes in recommendations from the early Guidance TA 19. 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.
- 2.10. 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.
- 2.11. 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.

- 2.12. The Panel considered all the above points, and found that there was no evidence undue rigidity in applying the cost per QALY approach. Rather, the Committee had worked extensively to incorporate adjustments in many different areas in order to present the most optimistic interpretation of the data reasonably open to it. They found the explanations given by the Appraisal Committee to be fair and transparent. They considered that there was sufficient explanation in the FAD to satisfy the need for transparency (paragraphs 4.2.6.1 to 4.2.6.8 inclusive).
- 2.13. The Appeal Panel found no inconsistency in the differences between TA19 and the current FAD, and noted that the Appraisal Committee was not required to justify these differences in the FAD. Nonetheless, they considered that the explanations given in paragraphs 4.3.10.7 and 4.3.10.8 incorporated sufficient reasoning to explain the adoption of the subgroups based on severity, and the rejection of a subgroup based on initial responders in the recommendations.
- 2.14. The Panel concluded that, although there was a degree of uncertainty concerning the QALY calculations and the measurement of health related quality of life, the Committee had reduced the risk of that uncertainty as far as possible through testing and upward adjustment, and that they had explained their deliberations adequately in the FAD.
- 2.15. Appeal Point 3.1 was therefore dismissed.

3.2 There is a lack of transparency in relation to the appraisal process.

3.2.1 There has been incomplete disclosure of the cost effectiveness model relied upon by the Appraisal Committee.

- 2.16. The Appeal Panel considered the Note to the Appeal Panel (6th July 2006) from the Chief Executive of NICE, and the response from EISAI (12th July 2006), as well the initial appeal letter.
- 2.17. The Appeal Panel questioned the Chief Executive of NICE regarding the Institute's refusal to disclose an executable version of the model.
- 2.18. The Panel heard that NICE held the view that it was not necessary for consultees to quality assure NICE, and that NICE is in a unique position amongst all the stakeholders as it holds the responsibility for the guidance it issues. The Chief Executive asserted that it was for the Appraisal Committee and the Guidance Executive to make judgments

about how data are used and shared, and to ensure that consultees are sufficiently informed so they can comment adequately.

2.19. The points raised by the appellant in their letter of 12th July are taken in turn:

1.1 The Institutes description of the model and its importance in the context of this appraisal are misleading.

2.20. The Panel heard that a wide number of inputs had been employed, and that the key elements are captured in the FAD, for instance in paragraphs 4.2.5 and 4.2.6. The Chief Executive of NICE referred the Appeal Panel to Technical Report 1, where the assumptions used in modifying the model are described. The Appeal Panel formed the view that, taken with a description of the original model in the Assessment Report, there was sufficient information to enable the appellant to understand how the model had been modified.

1.2 The Institute's assertion that consultees may fully understand the model, without access to an executable version is incorrect.

2.21. The Chief Executive of NICE explained that, in the read-only model, the user can run a probabilistic analysis and identify incremental cost effectiveness ratios, although they cannot run sensitivity analyses. They can see the content of cells, though they cannot track formulae. In terms of being able to check stability, confidence limits are outlined in the Assessment Report and in Technical Report 1.

2.22. The Appeal Panel concluded that, whilst it was not possible for the appellant to check the accuracy of the cost effective calculations, there was sufficient interaction possible with the model to understand how the model operated, and comment adequately on the model. The Appeal Panel noted that the appellant had indeed commented on the model, along with other consultees, demonstrating meaningful engagement. The Panel accepted that it was not necessary for appellants to quality assure NICE, as NICE on the one hand and consultees on the other had different roles in developing the guidance. NICE must quality-assure any data or model which it takes into account. That is why manufacturers are required to provide an executable version of any model they put forward.

1.3 The confidentiality of the model should not preclude disclosure to consultees in the context of this appraisal

2.23. The Appeal Panel was advised that the executable version of the model was commercial-in-confidence, and that the Institute respected this requirement and similar restrictions supplied by others submitting

evidence. The Appeal Panel concluded that a read-only version of the model, taken together with other information available to the appellant, gave sufficient information for them to be able to comment. The Chief Executive of NICE further explained that, the fully executable model was made available to (selected) members of the Appraisal Committee on the express understanding that it was not shared with consultees. This was the case in general, with respect to the technology process, and in particular regarding the SHTAC model for Alzheimer's drugs. The Appeal Panel concluded that the confidentiality of the model did preclude the disclosure of the model to consultees in an executable form.

1.4 The Institute's assertion that the Assessment Groups would not be willing to provide models to the Institute if they could not do so within the existing parameters of confidentiality is incorrect.

2.24. NICE explained in clear terms that Assessment Groups would not be willing to provide models to the institute if they could not do so within the existing parameters of confidentiality. The Appeal Panel accepted that this reflected the reality of the position.

2.25. The appellant sought to raise a number of arguments as to why Assessment Groups' intellectual property rights would not be infringed by disclosure of an executable version of an economic model. As set out above, however, the point raised by NICE is in the first instance a practical one: unless the existing parameters of confidentiality are maintained, Assessment Group will not be willing to provide models. In any event, the appellant's arguments based on intellectual property rights do not stand up to scrutiny.

2.26. They appellant first seeks to rely on section 45 of the Copyright, Designs and Patents Act 1988 ("**the 1988 Act**") as the basis for an argument that the Assessment Group's intellectual property rights would not be infringed if an executable version of the model were disclosed. Section 45(1) of the 1988 Act provides that, "*Copyright is not infringed by anything done for the purposes of parliamentary or judicial proceedings*". "*Judicial proceedings*" are defined in section 178 of the 1988 Act so as to include, "*proceedings before any court, tribunal or person having authority to decide any matter affecting a person's legal rights or liabilities*". The work of the Appraisal Committee in appraising technologies and formulating guidance does not constitute "*judicial proceedings*" for these purposes. The appellant suggests that the Appraisal Committee's work constitutes "*judicial proceedings*" because NICE may be susceptible to judicial review. This is a *non sequitur*. Many non-judicial, administrative bodies are susceptible to judicial review.

2.27. The appellant suggests that, as a consultee, it has an implied licence to use the Assessment Group's model. However, no basis is provided for this assertion.

2.28. Finally, the appellant suggests that it is entitled to an executable version of the model by virtue of section 30(1) of the 1988 Act. Section 30(1) provides, "*Fair dealing with a work for the purpose of criticism or review, of that or another work or of a performance of a work, does not infringe any copyright in the work provided that it is accompanied by a sufficient acknowledgement and provided that the work has been made available to the public.*" However, section 30(1) is of no relevance in the present context as an executable version of the Assessment Group's model has not been made available to the public.

1.5 NICE's concerns that disclosure of an executable version of the model would be burdensome for the institute are irrelevant.

2.29. The Appeal Panel considered that questions of proportionality and timing were relevant. It is important for the Appraisal Committee to keep to the appraisal timetable so as to ensure that the NHS is provided with timely and relevant guidance.

2.30. The Appeal Panel considered all the points above, and concluded that "read only" disclosure of the cost-effectiveness model was permissible and justified, and that the Appraisal Committee and NICE had been sufficiently transparent to allow the appellant to engage meaningfully in the appraisal process.

2.31. Appeal point 3.2.1 was therefore dismissed.

3.2.2 The FAD does not explain the Appraisal Committee's unqualified acceptance of the data from the controversial AD2000 study.

2.32. The Appeal Panel questioned the Appraisal Committee members regarding the AD2000 study, and were advised that the AD2000 study did not receive unqualified support; it did not contribute to the metanalysis performed by the Assessment Group, or the model used. The Chairman of the Appraisal Committee was aware that it had attracted criticism by experts (such as 40% drop out rates, ethical concerns, inclusion of patient groups with mixed disease, re-randomisation at three months and that the study was underpowered), and agreed with some of that criticism. For these reasons it was not a particularly influential part of the evidence. However, the AD2000 study did contribute to the evidence base: it was the only long term trial, it provided corroborative evidence to support the

'no drug effect', and was included in the analysis as a qualifier to caution against over-optimism.

2.33. The Panel were satisfied that the Committee had in fact been very cautious in considering the data from the AD2000 study, and had given it correspondingly reduced weight. The reference in paragraph 4.3.11 of the FAD served to demonstrate that not all the evidence pointed in the same direction, and the AD2000 trial was used as an example.

2.34. Appeal point 3.2.2 was therefore dismissed.

3.2.3 It is unclear whether and if so how the proposed guidance takes account of government policy, as reflected in National Service Frameworks and the quality outcome framework of the General Medical Services Contract.

2.35. The appellant clarified that this point related to transparency. The Appraisal Committee Chairman confirmed that the Committee had assessed the technologies within the wider framework of the National Service Framework for Older People (paragraph 2.8 of the FAD), and the dementia Guidelines Development Group. Members of the dementia Guidelines Development Group were present throughout the deliberations of the Appraisal Committee. Memory clinics were also mentioned in paragraph 4.3.5 of the FAD, although the Chairman of the Appraisal Committee stressed that the scope of the FAD did not include the merits of memory clinics: that was a matter for the dementia Guideline Development Group.

2.36. It was not clear from the written appeal letter how the appellant believed that the quality and outcomes framework of the General Medical Services Contract should have been taken into account, and they were unable to clarify this point at the appeal hearing. This point was therefore not pursued.

2.37. The Panel considered that it was clear from paragraph 2.8 of the FAD that the Committee were mindful of Government policy, as embodied in the National Service Framework for Older People, whilst ensuring they did not consider issues outside the scope of this appraisal.

2.38. Appeal point 3.2.3 was therefore dismissed

3.2.5 NICE has refused to disclose the summaries of the data and presentations given to the Appraisal Committee.

2.39. The appellant had responded in writing (Eisai's response to the Institute's Note to the Appeal Panel July 12th 2006) to the explanations given by the Institute as follows:

2.1 The summaries of the data and presentations do not constitute a record of the Committee's discussions.

2.2 The fact that the ACDs and FADs contain a review of the evidence does not relieve the Institute of its obligation to disclose the evidence relied upon in preparing such ACDs and FADs.

2.3 The Institute's assertion that disclosure of the requested material would expose the Institute to requests for clarification was implausible.

2.40. On questioning the Appraisal Committee, the Appeal Panel were informed that the summaries and presentations were working documents drafted for the Committee to remind them of the point they had reached in previous discussions, and as a substitute for the spoken word. Specifically, the Panel were questioned regarding whether the summaries or presentations contained any new material, and they were informed that they did not. Any new evidence presented to the Committee was disclosed. However, in order to maintain transparency of process, the Appraisal Committee does disclose a written overview for the first meeting of the Committee. This is specifically written for a wider audience. The other summaries are intended only for the Committee who were part of the discussions to which the summaries related. The Panel heard that these documents were, therefore, different in style and content.

2.41. Regarding the appellant's concern that the summaries and presentations would include the necessary selection (and perhaps omission) of particular data to present to the Committee, the Committee Chairman responded that this would be a reasonable concern if the overview was not shared with the consultees, but that as it was, he was satisfied that there was not a risk of the Committee missing evidence.

2.42. The appellants disagreed with the assertion that wider dissemination of the summaries and presentations would generate a large volume of enquiries. The Panel enquired of the Committee why they believed this would be the case, and heard that, because the documents were designed for the Committee, they would not be clear to other parties who had not hitherto been part of the deliberations. They believed, therefore, that there would be requests for clarification of the documents.

2.43. The Panel were satisfied that the summaries and presentations constituted working papers for the Committee and, in view of the fact that they contained no new evidence, there was no obligation upon the Committee to share them with consultees. The Panel was also mindful

that consultees have a number of substantive opportunities to participate and make representations during the appraisal process. The Panel did not accept that the consultees should have a right of access to, and participation in, every single stage in the Appraisal Committee's work.

2.44. Appeal point 3.2.4 was therefore dismissed.

3.2.5 It is unclear how the limitations in application and interpretation of MMSE scores have been taken into account by the Appraisal Committee in determining the threshold at which treatment with AChEIs should commence and be discontinued.

2.45. 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 TA19, and was accepted by all parties in that instance.

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

2.47. However, the Appraisal Committee had recognised the limitations of using MMSE scores (paragraph 4.3.13 in the FAD): the MMSE is a screening tool and is 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 of flexibility in interpreting MMSE scores.

2.48. 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 should be treated differently from the population as a whole.

2.49. 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.

- 2.50. 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.
- 2.51. The Committee had deliberated as to whether to soften the subgroup thresholds by including words such as 'normally' or '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.
- 2.52. 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.
- 2.53. The appellant raised the concern that the MMSE varied over time. The Appeal Panel noted that the FAD did not specify how often the MMSE should be measured in determining an individual's position in relation to the threshold. The Committee stated that this was a matter for the Guidelines Development Group to consider. The Panel believed this to be appropriate, and noted that there was nothing in the FAD to suggest that clinical decisions should be made on a single assessment using the MMSE.
- 2.54. The Appeal Panel concluded that the Committee had acknowledged and addressed the limitations in application and interpretation of MMSE scores, and had described their reasoning adequately in the FAD, (paragraph 4.3.13).
- 2.55. However, they did consider that the last sentence in paragraph 4.3.13 did not fully reflect the intended meaning of the Committee, and so referred this point to the Guidance Executive for their consideration.
- 2.56. Appeal point 3.2.5 was therefore dismissed

3.2.6 There is no explanation for the Appraisal Committee's rejection of the assessment of cost effectiveness based on response to treatment, consistent with NICE's original Guidance of 2001 in the context of the proposed recommendations at paragraph 1.1 of the FAD.

2.57. 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 TA 19. 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 placebo.) 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.

2.58. 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.

2.59. 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 lead to the treatment of greater numbers of people who would not benefit from treatment.

2.60. The Panel concluded that the Appraisal Committee had deliberated on the merits of the various subgroup possibilities in attempting to identify maximum cost effectiveness, and had outlined their conclusions in paragraph 4.3.10.7 of the FAD, as well as outlining the process leading to their conclusions in paragraphs 4.2.6.5 and 4.2.6.6.

2.61. Appeal point 3.2.6 was therefore dismissed.

3. Ground 2

3.1. The appellant raised in correspondence an anomaly they believed to be a factual error, and were invited to raise it under Ground 2. The appellant

asserted that, in paragraph 4.1.2.5 of the FAD, the first sentence should read "...although these findings were not statistically significant in all of the trials (as opposed to any of the trials, as currently written in the FAD). The Appraisal Committee members confirmed that the sentence should read 'all of the trials'.

3.2. The Appeal Panel is therefore referring this point to the Guidance Executive for consideration.

4.1 The exclusion of patients with mild Alzheimer's disease from treatment does not reflect the benefits of therapy, is arbitrary and therefore perverse.

3.3. The Panel questioned the Appraisal Committee members regarding the differential benefits in the mild and moderate groups, and heard that, although there was a statistically significant improvement in both the mild and the moderate groups, the subgroup analysis demonstrated a greater magnitude of 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.

3.4. The Committee agreed that the drugs are still 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.

3.5. The appellant's assertion was that the Committee's analysis did not reflect the benefits of treatment for people with mild Alzheimer's disease.

3.6. The appellant asserted that the model did not capture the benefits of treatment to patients with mild Alzheimer's disease. The Panel enquired of the Appraisal Committee members why they believed the model accurately reflected the benefits to people with mild disease. The Appraisal Committee Chairman explained that the original model, without adjustments, had produced CQG figures approaching UK£100,000. It was only through identifying subgroups that a group of patients were identified for whom treatment would be cost effective. Any further manipulation that

moved resources back towards the mild group would render treatment for both groups cost-ineffective.

- 3.7. The appellant asserted that the guidance deprived patients with mild Alzheimer's disease of treatment because the substantial costs are borne primarily by families and carers, and that this was unacceptable. The Panel noted that the Appraisal Committee was required to conduct the evaluation from the perspective of the NHS and PSS decision-maker. The Panel believed that the approach taken by the appraisal Committee was consistent with the wider funding issues regarding NHS and PSS.
- 3.8. The reasons given to the Panel as to why the responder analysis was rejected by the Appraisal Committee are detailed under Ground 1.
- 3.9. The appellant believed the Committee had misunderstood the non-linearity of the relationship between MMSE scores and the progress of the disease. In response to questioning, the Appraisal Committee Chairman confirmed that there was good evidence of a linear relationship between MMSE and HUI2 (measuring function). It followed that there was not a risk of taking an unduly adverse view of the mild group in assessing the benefits of treatment (see 3.1 under Ground1).
- 3.10. The appellant asserted that the SHTAC model assumes no additional treatment benefit beyond a 6 month period. In response to questioning, the Committee members asserted that in fact the SHTAC model did allow for cumulative benefit (incorporated into the risk equations used). The Panel noted that the Committee acknowledged some divergence between the treated and non treated groups over 2-3 years, but that these two groups converged after five years. Regarding the Nordic trial, the Committee recognised that there did appear to be apparent accumulated benefit, but that this was one trial, and many other trials showed no accumulated benefit. The Nordic trial needed to be taken into account alongside the other data presented to the Committee. They also advised that open-label extensions needed to be treated with great caution. Furthermore, as the technologies were not disease-modifying drugs, there was unlikely to be significant cumulative benefit.
- 3.11. The Panel informed the appellant that the new data analysis from the Nordic trial that was submitted to the Appeal Panel in the appeal letter would not be considered, as the Appraisal Committee had not had access to this analysis during their deliberations.
- 3.12. The Panel ascertained that the Committee had investigated subgroups in order to ascertain whether there was a subgroup of patients for whom the technologies were more cost effective, thus enabling the Committee to recommend the technologies for this subgroup. The

Committee Chairman emphasised that, without the subgroup analysis, the technologies would NOT be recommended for people with mild and moderate Alzheimer's disease, because they were not cost effective for the group as a whole. Thus, identifying the greater benefit (and thus improved cost effectiveness) of the moderate disease group enabled the Committee to move from recommending no treatment to recommending treatment for those with moderate and moderately severe Alzheimer's disease.

- 3.13. The Panel ascertained that differentiation of the subgroups defined as mild, moderate, and moderately severe reflected clinical practice and was possible to implement.
- 3.14. The Panel formed the view that, in identifying the moderate and moderately severe subgroups as the group that would benefit most from the technologies, the Committee had ensured that the technology 1) was available 2) was targeted most effectively, and 3) delivered acceptable cost effectiveness. The Panel was advised that any resource shift from the moderate to the mild group rendered treatment for both groups cost-ineffective.
- 3.15. The Panel therefore concluded that the Committee had argued cogently and logically in reaching their conclusions, and that these conclusions were not perverse.
- 3.16. Appeal point 4.1 was therefore dismissed.

4.2 The statement in the FAD that 'the discontinuation level of MMSE is set by the AChE inhibitor licence' is incorrect

- 3.17. The Appraisal committee Chairman acknowledged that the sentence in 4.3.13 that referred to the AChE inhibitor license could be better worded, to reflect the intended meaning of the Committee.
- 3.18. This point was therefore referred to the Guidance Executive for their consideration.

4.3 The Direction in the FAD that treatment should be withdrawn at an MMSE score of 10 irrespective of continued benefit is perverse.

- 3.19. The Appeal Panel questioned the Appraisal Committee Chairman as to whether the Committee believed there was ever a situation where treatment might continue in a patient whose MMSE score was less than 10. The Chairman acknowledged that this was possible, and recognised that it was a matter of individual clinical judgment to continue treatment when appropriate. Such flexibility in applying the guidance was covered

by the 'context' statement present in all guidance published by NICE: 'guidance does not...override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.'

3.20. The Appeal Panel considered that the guidance was written so as to give a clear recommendation, but that the 'context' statement allowed for individual cases to be assessed, and the guidance overruled, where necessary.

3.21. Appeal point 4.3 was therefore dismissed.

4.4 In the context of the accepted unreliability of the SHTAC cost-effectiveness model, reliance upon it to determine whether or not patients may receive NHS treatment with AChE inhibitors is perverse

3.22. The Appeal Panel considered that the uncertainties inherent in the model had been addressed, by testing the model against others, by moving data to more optimistic scenarios, and by augmenting the model as described in the FAD, (see appeal point 3.1 under Ground 1). They recognised that the original model rendered the technologies cost-ineffective, and that amendments to the model had served to bring the costs down to a utilisable level (see appeal point 4.1 under Ground 2)

3.23. The Appeal Panel considered that the Committee had utilised the best available model, and had taken extensive measures to eliminate the potential negative effects of uncertainty, and to define a cost effective subgroup. Without this reworking the technologies would have been cost-ineffective for all people with Alzheimer's disease. The Panel concluded that there was no perversity in the behaviour, reasoning or decisions of the Committee.

3.24. Appeal Point 4.4 was therefore dismissed.

4.5 The statement in the FAD that the effect of donepezil on behavioural symptoms is 'less clear' is not consistent with the available evidence (see paragraph 4.1.2.14 of the FAD)

3.25. The Appeal Panel determined that the statement in 4.1.2.14 was an acceptable paraphrasing of paragraph 4.1.2.7, which states that the four RCTs produced varied results, but a small and statistically significant effect for donepezil on behavioural symptoms.

3.26. Appeal point 4.5 was therefore dismissed.

4. Ground 3

5.1 The institute has prepared Guidance that is outside the remit and scope of this appraisal by stating at para 1.1 that AChEi medication “should only be continued while the patient’s MMSE score remains at or above 10 points...”

- 4.1. The Appeal Panel heard from the Appraisal Committee Chairman that the Committee was not seeking to comment on the use of the technologies outside their licence, and was certainly not making recommendations for off-licence use.
- 4.2. The Appeal Panel considered that the wording in paragraph 1.1 described the use of the technologies within the moderate and moderately severe phases of Alzheimer’s disease, and was not making a comment on the use of the technologies in patients with severe disease.
- 4.3. The Appeal Panel concluded that the Institute had not prepared Guidance outside the remit and scope of the appraisal.
- 4.4. Appeal point 5.1 was therefore dismissed.

5.2 The Institute’s use of thresholds for commencement and discontinuation of treatment with AChEIs, based on MMSE scores, breaches Article 14 of the European Convention on Human Rights.

- 4.5. The appellant contended that the use of MMSE scores to define treatment thresholds constituted a breach of Article 14 of the European Convention on Human Rights (“ECHR”), which provides that, *“The enjoyment of the rights and freedoms set forth in this Convention shall be secured without discrimination on any ground such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status.”*
- 4.6. Article 14 may be invoked only in conjunction with another Convention right.. Unless the matter complained of falls within the ambit of another Convention right, Article 14 cannot be breached. The appellant sought to rely upon Article 2 (the right to life), Article 3 (the prohibition on torture and inhuman and degrading punishment) and Article 8 (the right to respect for private and family life, home and correspondence) of the ECHR. The Appeal Panel recognised that it is not necessary to show a breach of any of these Articles for Article 14 to be invoked. However, it concluded that the definition of treatment thresholds for the AChEIs by reference to MMSE scores did not even fall within the ambit of any of these Convention rights. These are not life-saving drugs. Nor do they

prevent the decline of patients with Alzheimer's disease. At best, they ameliorate the condition of some individuals with the disease to some extent, for a relatively short period of time. The guidance is consistent with all patients having access to the drugs at some stage in the progress of their disease. In those circumstances, the Appeal Panel concluded that the treatment thresholds set out in the FAD did not fall within the ambit of the right to life, the prohibition on inhuman and degrading punishment or the right to respect for private and family life.

4.7. In any event, the Appeal Panel was not persuaded that the FAD would be discriminatory in effect. It noted that no evidence as to the nature and extent of any alleged discriminatory effect was advanced by the appellant. It was accepted by the Appraisal Committee that use of MMSE scores alone might disadvantage certain individuals. However, the Panel concluded that the guidance would not have a significant discriminatory effect 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.

4.8. Further, to the extent that any residual discriminatory impact might arise from the guidance, the Panel considered that any such outcome would be justified and proportionate. Any residual discriminatory impact would be likely to be small, particularly if practitioners are seeking to exercise their clinical judgment properly. Moreover, 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. Given NICE's statutory duties, and in particular its important role in providing clear and workable guidance to the NHS, therefore, any residual discriminatory effect would in the Panel's view be pursuing a legitimate objective, and would be justified and proportionate to the aims of such guidance.

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

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

5.2. 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.