

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Appeal by Shire Pharmaceuticals 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: Shire Pharmaceuticals Limited.
- 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.

1.6. 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.

1.7. 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.

1.8. 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 the 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.

1.9. 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.

1.10. 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 conclusion that 30% of patients should be removed from the cost equation on the basis that that percentage of the cost of nursing/residential care is met by people with AD is unfair because it is inconsistent with the Perspective set out the Guide to Manufactures and Sponsors, June 2001.

2.1. The Panel enquired of the Appraisal Committee whether they had considered the implications on cost effectiveness if 100% of nursing/residential care costs were included. The Committee had run the model using this figure, but had not used it because it was not within the scope of the guidance. In the appraisal process, many private payments are not included in cost effectiveness estimates of technologies. The only ones that are included are specific patient contributions to the NHS or PSS budget, as noted in the Guide to Manufacturers and Sponsors:

2.2. "The recommended perspective includes all resource use funded by NHS and PSS budgets (including any element of those budgets contributed by patients)".

2.3. The Panel accepted that the intended meaning of this statement was that only patient contributions specifically to the NHS/PSS budget should be taken into account. It did not include other private expenses. The Panel had sympathy with the appellant's point, but recognised that any inherent unfairness regarding how private funding was taken into account existed within the wider NHS. In this context, the Committee had acted fairly towards the appellant (and consistently with respect to other appraisals) and in accordance with published procedures, specifically the Guide to Manufacturers and Sponsors, June 2001.

2.4. The appellant made the point that full PSS costs were included in pre full term care costs, and there was therefore inconsistency in how the costs were applied. The Committee Chairman responded that they had followed the advice of the Assessment Group. In any case, the user contribution was not a substantial element of pre full term care costs.

2.5. The Panel noted the anomaly, but recognised that, even if there had been inconsistency, the material outcome of the guidance was not affected as the size of the effect was small.

2.6. Appeal point 1 was therefore dismissed.

2. The Committee has used data outside the scope of the appraisal.

2.7. The Panel questioned the Appraisal Committee Chairman as to why they had considered evidence relating to doses of galantamine not used in a clinical setting. The Chairman stated that the Committee was aware that, in citing 44% adverse effects, the data had included one trial where twice the usual daily dose of galantamine was used (paragraphs 4.1.3.4 and 4.1.3.6). Paragraph 4.1.3.6 states clearly that, from the trial data, the number of participants withdrawing from the trial because of adverse events increased with higher doses of galantamine. However, it was also noted in the FAD (paragraphs 4.1.3.2 and 4.1.3.11) that the benefits varied with the dose of galantamine. Both benefits and adverse events needed to be included as part of the assessment of the technology's effects.

2.8. The Panel noted that the Assessment Report (and the corresponding part of the FAD titled 'Consideration of the Evidence') addressed all the evidence that may be relevant. Recommendations for clinical use were not included in this section. Nowhere in the FAD were recommendations made to use galantamine outside of its licence.

2.9. In paragraph 4.1.3.11, the Panel were not sure what the words 'considerably more' referred to. The Committee Chairman confirmed that this should read 'considerably more participants than those on placebo withdrew because of adverse events.'

2.10. The Panel concluded that the Committee had been fair in presenting the evidence as written in the FAD.

2.11. Regarding the wording in 4.1.3.11, the Panel referred the point to the Guidance Executive for their consideration. In other respects appeal point 2 was dismissed.

3. Ground 2

3 and 3.1 The conclusion reached for recommending treatment to moderate patients but excluding new mild patients arises from such a distortion of the available clinical and cost effectiveness evidence that the guidance is perverse.

3.1. The appellant emphasised the clinical effectiveness of the technologies for people with mild disease. In particular they cited two studies – Galasko et al (1997) and Feldman et al (2005) - which supported the

notion that the negative impact of mild Alzheimer's disease was significant. The Appraisal Committee confirmed that the Assessment Group had considered both of these studies, but that the Galasko paper had been excluded as it did not meet the inclusion criteria set by the Assessment Group.

- 3.2. The Appraisal Committee recognised the impact of mild disease on patients and the Appeal Panel noted that the clinical effectiveness of galantamine in relation to those with mild Alzheimer's disease was not in question. The recommendations to treat only moderate patients rested on the cost effectiveness of the technologies.
- 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 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 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.
- 3.6. 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).

- 3.7. 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 to those with moderate and moderately severe Alzheimer's disease.
- 3.8. The Panel ascertained that differentiation of the subgroups defined as mild, moderate, and moderately severe reflected clinical practice and was possible to implement.
- 3.9. 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 was 1) available 2) 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.
- 3.10. The Panel therefore concluded that the Committee had argued cogently and logically in reaching their conclusions, and that these conclusions were not perverse.
- 3.11. Appeal point 3.1 was therefore dismissed.

3.2 The assumptions in the model on which the Committee has made its recommendation postulate that there is no treatment benefit after six months and that a rate of untreated decline applies to treated patients after six months. Neither assumption is correct and these errors are perversely perpetuated in the FAD.

- 3.12. The appellant asserted that the SHTAC model assumes no additional treatment benefit beyond a 6-month period. In response to questioning, the Committee members responded that in fact the SHTAC model did allow for the possibility of cumulative benefit (incorporated into the risk equations used). The Committee recognised that there did appear

to be accumulated benefit demonstrated in some trials, but many other trials showed no accumulated benefit. The Committee needed to take into account all the evidence. There was no long-term randomised evidence and open label studies suffered from non-random attrition.

- 3.13. The Committee had concluded that there was no reliable evidence to support the notion of cumulative benefits from early treatment.
- 3.14. Furthermore, they argued that, as the technologies were not disease-modifying drugs, there was unlikely to be significant cumulative benefit.
- 3.15. The Panel recognised that there was a difference of opinion between the Appraisal Committee and the appellant as to which data were most reliable.
- 3.16. However, the Panel concluded that the Committee had reached a reasoned decision in rejecting the certainty of accumulated benefit or decreased rate of deterioration after six months treatment. Neither their reasoning nor their decision was perverse.
- 3.17. The appellant asserted that the FAD was incorrect in stating that the Committee was not initially provided with any evidence that could have identified this subgroup prospectively (paragraph 4.3.10.8). The Committee Chairman recognised this inaccuracy, but stated that the intention of the Committee was to state in the FAD that the Committee was not initially provided with any *robust* evidence.
- 3.18. The Appeal Panel referred this point to the Guidance Executive for their consideration regarding paragraph 4.3.10.8. Subject to this point being resolved, Appeal point 3.2 was dismissed.

3.3 Mortality estimates used in the institute’s model are not tested against objective actual patient data despite such data having been available to the Institute for over a year. The adoption of a crude annual rate rather than an objectively verifiable basis of estimating mortality arbitrarily underestimates the cost effectiveness of galantamine in mild patients.

- 3.19. The Committee considered that the original risk equation for mortality from the AHEAD model was considered too low to represent a population with mild to moderately severe Alzheimer’s disease (paragraph 4.3.10.5 of the FAD). The Committee Chairman described how the Committee had considered the Assessment Group’s estimate on mortality, and other estimates, and found that there was evidence to suggest variance in mortality in either direction: some estimates were less

favourable, with mortality rates up to 18%. They therefore took the view that an annual rate of 11.2% was reasonable.

3.20. The Assessment Group used a constant mortality rate irrespective of age and severity. The Panel questioned the Committee Chairman as to why the Committee had accepted the Assessment Group's estimate. A sensitivity analysis had been performed, and changes in annual mortality rate only marginally affected cost effectiveness estimates. The Chairman accepted that there probably was a differential rate of mortality with disease progression, but that did not entail that the model overestimated mortality, even at the mild stage of the disease.

3.21. The Panel noted that, once again, there was disagreement between the appellant and the Committee as to which data was most valid. However, the Panel recognised that the Committee had considered a range of estimates, and that changes in mortality rate affected cost effectiveness only marginally. They considered there was no perversity in adopting an annual mortality rate of 11.2%

3.22. Appeal point 3.3 was therefore dismissed.

3.23. The appellant requested that the references regarding mortality rates be made available. The Chairman of the Appraisal Committee agreed to provide these.

4. The FAD perversely fails to take into account, discounts unreasonably, or otherwise fails to explain what account has been taken of data to support conclusions on global outcomes, adverse event withdrawal and long term effectiveness.

3.24. The appellant asserted that two relevant RCTs were excluded. The Committee members responded that the Tariot (2000) trial was included, and the Brodarty (2005) trial was not included in the meta-analysis performed by the Assessment Group. Not enough detail was provided in relation to these trials for them to be included.

3.25. The Panel noted that the evidence regarding global outcomes was described in 4.1.3.3 and 4.1.3.4, and adverse events in paragraph 4.1.3.6. As previously described, the Committee members had determined that, overall, there was inconclusive evidence regarding long term effectiveness.

3.26. The appellant and Appraisal Committee members agreed that, in paragraph 4.1.3.3. of the FAD, the aggregate number of people randomised should be 2294.

3.27. The Panel concluded that, although there was disagreement about how this data was interpreted, the Appraisal Committee had not unreasonably excluded relevant evidence, or otherwise acted perversely in their deliberations.

3.28. Appeal point 4 was therefore dismissed.

5. The FAD takes into account irrelevant considerations and fails to take into account relevant considerations, in regard to a wide array of cost inputs for the model, leading to perverse conclusions (in particular at paragraphs 4.3.6 and 4.3.7). Among other things, the exclusion of 30% of the costs of institutional care representing those who pay for the costs of their care is perverse.

3.29. The Appeal Panel judged that this point amounted to a disagreement over the approach taken by the Assessment Group in its choice of assumptions. In considering a range of data, the Appraisal Committee increased the costs of full-time care and reduced the costs of pre-full-time care, thereby changing the assumptions in a manner more favourable to the technologies. The Panel considered that the reasons for rejecting the manufacturers' cost effectiveness calculations itemised in paragraph 4.3.6 were reasonable, and that the Committee's preference for the Assessment Group model was clearly argued in 4.3.7. The Panel concluded that there was no perversity in choosing the Assessment Group's model to assess cost effectiveness.

3.30. The arguments regarding private institutional care are rehearsed under point 1. The Panel believed the Committee was acting within the scope and in accordance with the Guide to Manufacturers and Sponsors (2001), and therefore could not be judged to have acted perversely.

3.31. Appeal point 5 was therefore dismissed.

6. The selection of a time horizon of five years rather than seven years led to a perverse treatment of the evidence.

3.32. In response to questioning, the Committee Chairman explained that the time horizon of five years had been used in the original model. Although he accepted that there was a group of patients who would live longer than five years, this group was off-set by those who would not live for five years. In those circumstances, a time horizon of five years was considered to be reasonable. The Appeal Panel accepted that this was a reasonable basis for the selection of a time horizon of five years, and rejected the contention that it was perverse.

3.33. Appeal point 6 was therefore dismissed.

7. There are factual inaccuracies in the FAD which illustrate a perverse approach to the evidence.

- 3.34. The appellant listed a number of points which they believed were factually inaccurate. The Panel questioned the Committee members on each in turn. The Committee members agreed that the FAD held factual inaccuracies in paragraphs 3.3, 4.1.3.1, 4.1.3.2, and 4.1.3.4, as outlined by the appellant in paragraphs 7.1, 7.2, 7.3, 7.4, and 7.5 of the appeal letter.
- 3.35. The Panel considered that these were simple errors and did not alter the material outcome of the FAD.
- 3.36. The points raised by the appellant in paragraphs 7.6, 7.8, 7.11, have been dealt with elsewhere in this appeal decision letter.
- 3.37. Points raised by the appellant in paragraphs 7.7, 7.9, 7.12 are not factual inaccuracies, but reflect the appellant's difference of opinion from that stated in the FAD.
- 3.38. With respect to the factual inaccuracies acknowledged, the Panel referred appeal point 7 to the Guidance Executive for their consideration. Subject to resolution on the inaccuracies, appeal point 7 was dismissed.

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

- 4.1. Subject to the points referred to the Guidance Executive for consideration, the Appeal Panel has dismissed the appeal on all points.
- 4.2. 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.