

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

### Appeal by Lundbeck 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: Lundbeck 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. 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 Alzheimers 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 has unfairly rejected the statistical validity of the subgroup of behaviourally disturbed people with moderately severe to severe Alzheimers Disease.**

- 2.1. The Appeal Panel questioned the Appraisal Committee Chairman as to why they had challenged the statistical validity of the subgroup, particularly given that they had accepted the subgroups identified for the AChE inhibitors. The Chairman explained that the subgroup was rejected both in statistical and clinical terms. The difficulty in distinguishing the group clinically was judged to be the primary point by the Committee. Both points are made in paragraph 4.3.17 of the FAD.
- 2.2. The evidence base for memantine was much smaller than that for AChE inhibitors, comprising only three trials. One of the trials had not been submitted to the Appraisal Committee until after the Assessment Report had been produced. The three trials had conflicting results; overall it was the Committee's conclusion that clinical effectiveness was not proven. It was therefore from a very different perspective to that of the AChE inhibitors that subgroup analysis was investigated.
- 2.3. The meta-analysis performed on the AChE inhibitors identified distinct subgroups. The meta-analysis performed by the manufacturer used a different technique, but the advice from the MRC Biostatistics Unit was that the groups were not sufficiently distinct for the purpose of defining clinical or cost effectiveness (paragraph 4.3.17 of the FAD). Clinically, the behaviourally disturbed subgroup identified by the manufacturers (NeuroPsychiatric Index (NPI)>1) was considered by the Committee to be such a wide definition that it was unusable in interpreting data. Committee members stated that the Committee recognised the behaviourally disturbed subgroup as clinically distinct, but the definition used by the manufacturer was very unreliable clinically. The Committee member stated that they would not define a subgroup in such a loose way.
- 2.4. The Appeal Panel noted that the Appraisal Committee's assessment of the three trials put memantine 'on the margins' of clinical effectiveness. Thus further efforts to define a subgroup were an opportunity to explore effectiveness further; the Committee was not required to perform subgroup analysis, or take particular heed of analyses performed by consultees. As with all post-hoc analyses, they needed to be treated with caution.

- 2.5. The Panel noted the conflicting views of the manufacturer and the MRC Biostatistics Unit, and were advised by the Committee members that the Committee, in the light of the conflicting views, took the cautious view, as there was not sufficient evidence to be sure of a subgroup effect.
- 2.6. The Panel noted that the Committee members emphasised that they were keen to identify a subgroup effect if at all possible, as the behaviourally disturbed subgroup was an important clinical group. The clinical experts giving evidence to the Committee were equivocal in their comments regarding the effectiveness of memantine.
- 2.7. The Panel believed that the Committee had sound reasons for rejecting the validity of the subgroup as defined by the manufacturers, and had outlined their reasoning in 4.3.17. They further noted that the Committee were not required to assess any subgroup analysis, but had done so in this case in order to be absolutely sure there was no hidden treatment effect.
- 2.8. The Panel concluded that the Committee had behaved fairly and in accordance with published procedures.
- 2.9. Appeal point 1 was therefore dismissed.

**2. The Appraisal Committee has unfairly excluded good quality evidence of clinical effectiveness from the MD-02 trial. No reasons are given for the exclusion of this data.**

- 2.10. The Appraisal Committee Chairman stated that he had checked with the MRC statistician, and that they had confirmed that they had included all three studies in their analysis.
- 2.11. In view of the uncertainty surrounding this issue, the Appeal Panel Chair requested that the Chairman seek written clarification from the MRC Biostatistics Unit as to what had (and had not) been included in their analysis.
- 2.12. Subject to the above being resolved satisfactorily, appeal point 2 was dismissed.

**3. The Appraisal Committee unfairly denied Lundbeck an opportunity to consult within the appraisal process.**

- 2.13. The Panel questioned the Committee members regarding the opportunities to consult. At the end of part one of the appraisal process, comments on the Appraisal Consultation Document (ACD) are invited. In

the case of this appraisal, where there were two ACDs, this opportunity arose twice. The process has been the same as for all other appraisals. If new evidence emerges between the publication of the ACD and the FAD, further comments are sought. Further comments are not invited on each stage of the Committee's deliberations.

2.14. Any consultee may request attendance at any committee meeting; permission is at the Chairman's discretion. The Panel were advised that in practice this does not usually appear to be necessary.

2.15. In addition, the Panel learned that the appellant had met with Institute staff, including the Chairman, on many occasions.

2.16. The Panel concluded that the appellant had had ample opportunity to consult within the appraisal process.

2.17. Appeal point 3 was therefore dismissed.

**4. The Appraisal Committee unfairly applied different criteria to the approval of a subgroup to memantine as compared to the other technologies in the appraisal. No reasons are given for treating memantine in a different way.**

2.18. The points raised are noted under appeal point 1. The Panel was satisfied that a fair process had been applied. The outcomes of the meta-analyses were different in the two technological groups. The MRC report was able to identify distinctly separate subgroups for the AChE inhibitors. This was not the case for memantine. The outcome of the appraisal of clinical effectiveness was also different for the two groups. Thus differences in subsequent treatment were predicated on this first step, i.e. different clinical effectiveness profiles.

2.19. The Panel was therefore satisfied that the appellant had been treated fairly.

2.20. The Appeal Panel dismissed appeal point 4.

**5. The Committee has unfairly rejected the specificity of the subgroup**

2.21. This point is dealt with under appeal point 1 above. In particular, the Panel noted that, although a clinically distinct subgroup, the manufacturer's definition was very wide and was therefore unusable of the purpose of identifying different treatment effects in the subgroup. Furthermore, the Committee was not required to examine the subgroup effect at all, especially in view of the doubtful clinical benefit identified.

The reasons for rejecting the specificity of the subgroup are outlined in paragraph 4.3.17 and 4.3.18 of the FAD.

2.22. Appeal point 5 was therefore dismissed.

**6. The Appraisal Committee has unfairly mischaracterised a comment made by another consultee (paragraph 4.3.17 of the FAD).**

2.23. This point is considered under point 13.

**7. The Committee has unfairly rejected evidence of the cost effectiveness of memantine because of its prior rejection of the validity and specificity of the subgroup.**

2.24. The Appeal Panel questioned the Appraisal Committee Chairman regarding the use of QALYs. 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 described in Technical Report 1, and the LASER-AD study (Livingstone et al 2004)

2.25. 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.

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

2.27. 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.

2.28. 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.

2.29. The appellant asserted that the threshold for acceptance of cost effectiveness should be set at a higher QALY value as carer proxies were used.

- 2.30. The Appeal Panel asked why the Committee had used the Health Utilities Index Mark 2 (Neumann 1999), which had not been evaluated in dementia, and was 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 any shortcomings in the use of this Index.
- 2.31. In terms of memantine, the Appeal Panel noted that the cost effectiveness of the subgroup was a secondary issue for consideration: the use of memantine for the group of moderately severe and severe sufferers of Alzheimer's disease as a whole failed the clinical effectiveness test. Further, the subgroup definition used by the manufacturers was unhelpful for the purpose of identifying treatment effect, and cost effectiveness was considered within the parameters set by this limited data (paragraph 4.3.18 of the FAD).
- 2.32. The Appeal Panel heard that the Committee had considered the memantine model, but had had a number of concerns, as explained in paragraphs 4.3.19 – 4.3.24 of the FAD. In particular, the Panel questioned the Committee as to why dependency could not be taken into account. The Committee Chairman responded that the Committee had considered the memantine model, which included cognition, institutionalisation and dependency. There were contentious issues in the calculation of all of these, but they were not independent of each other, and therefore the model included an element of triple counting.
- 2.33. The Panel concluded that the Committee had not relied solely on QALYs, and had sound reasons for rejecting the memantine model's calculations, particularly in respect of dependency. The Panel believed that the Committee's deliberations were adequately explained paragraphs 4.3.19-24 of the FAD. The Panel concluded that the Committee had acted fairly.
- 2.34. Appeal point 7 was therefore dismissed.

**8. The Committee has unfairly failed to consider an augmented base case for memantine when such a case forms the basis for the positive guidance on acetyl cholinesterase inhibitors.**

- 2.35. As described previously under point 1, the Panel noted that memantine had failed the first relevant test, namely that of clinical effectiveness. The Committee had, nonetheless, examined cost effectiveness in response to the evidence placed before them, and in order to treat all submissions with equivalence. However, given that clinical effectiveness had not been shown, either for the group as a whole

or for the behaviourally disturbed subgroup, there was no indication to attempt to establish improved cost effectiveness by augmenting the base case.

- 2.36. Secondly, the augmented base case was commissioned in order to acknowledge uncertainty around the model, and moved the model to a more optimistic possible outcome. The parameters in the augmented base case had arisen as a result of consultation on ACD1. No relevant comments had been received to suggest a different model for memantine. The standard consultation process had been applied to all consultees.
- 2.37. As carer time was not considered in the augmented base case, and reference to carer time saved with respect to memantine had been removed from the FAD, the Committee agreed that reference to carer time saved with respect to AChE inhibitors should also be removed, to preserve fairness (paragraph 4.1.3.7 of the FAD).
- 2.38. The Panel concluded that there were sound reasons for treating memantine differently from the AChE inhibitors in this respect, and that the Committee had been fair and transparent in its reasoning.
- 2.39. Appeal point 8 was therefore dismissed.

**9. The Committee has unfairly misrepresented Lunbeck's data from a responder analysis.**

- 2.40. Further to the agreement of the Panel, by letter dated 18 July 2006 the appellant made further comments relevant to this point. This letter highlighted that the second sentence in paragraph 4.1.6.7 of the FAD was inaccurate and should have been included in paragraph 4.1.6.6. The Panel acknowledged that this sentence should have been included in paragraph 4.1.6.6, and should have been subject to the caveat to the effect of, "*depending on choice of RCTs*". However, the Appeal Panel noted that this error was not material to the Appraisal Committee's fundamental reasons for not recommending the use of memantine, as set out above, and in particular the inadequacy of the definition of the behaviourally disturbed sub-group.
- 2.41. The Appeal Panel agreed with the Appraisal Committee's view that the second sentence of paragraph 4.1.6.7 of the FAD should be moved to paragraph 4.1.6.6, and should be subject to a caveat as referred to above. Accordingly, this point is referred to the Guidance Executive for consideration.
- 2.42. The Committee members acknowledged that the FAD is incorrect in paragraph 4.1.6.7. The second part of 4.1.6.7 starting "Differences in

the proportions.....” should be inserted into paragraph 4.1.6.6. before the final sentence, with an appropriate caveat.

2.43. The Panel referred this point to the Guidance Executive for their consideration.

### 3. Ground 2

**10. The guidance perversely fails to reflect the late concession made by the MRC statistician that Lundbeck’s method is an appropriate method, if not the most appropriate method for demonstrating such validity.**

**11. The guidance perversely prefers the evidence of the MRC Statistician’s meta-analysis to Lundbeck’s analysis based on individual patient level data taking into account all three trials.**

3.1. The Panel noted that it was the view of the Committee that the MRC Biostatistics Unit analysis, as reported in 4.3.17. was accurate, as it had been clarified that the MRC statistician had in fact used the data from all three trials (see appeal point 2 under Ground 1). Therefore there was no perversity in stating the views of the MRC Biostatistics Unit in paragraph 4.3.17 of the FAD.

3.2. The Panel was not persuaded that the MRC statistician had conceded that the Lundbeck model was an appropriate method, as the report identifies the lack of power in the meta-analysis, and the hypothesis that analysis of individual patient data may address this. However, even if her view was that the Lundbeck methodology was acceptable, it was not perverse of the Committee to use an alternative methodology, if they believed this to be more appropriate. The appellant appears to acknowledge this in its appeal letter (paragraph 48 bullet point 1).

3.3. The Panel concluded that the conduct and conclusions of the Committee were not perverse.

3.4. Subject to the written clarification requested from the MRC Biostatistics Unit in appeal point 2, appeal points 10 and 11 were dismissed.

**12. The Guidance perversely rejects the behaviourally disturbed subgroup as not specific enough on the basis of no evidence, when the evidence before it was that clinicians have no difficulty in identifying this subgroup.**

3.5. See also appeal point 1.

3.6. The Panel noted the distinction made by the Appraisal Committee members between the existence of a clinically distinct subgroup, and the methodology used to define it. The Committee considered the definition of an NPI>1 to be so loose as unusable in a clinical setting.

3.7. The Panel concluded there was no perversity in the conclusions of the Committee as noted in paragraph 4.3.17 of the FAD.

3.8. Appeal point 12 was therefore dismissed.

**13. The Guidance perversely relies on an observation of the Alzheimer's Society, taken out of context, in order to reject Lundbeck's definition of the subgroup.**

3.9. The appellant asserted that their comments had been taken out of context in paragraph 4.3.17 of the FAD. The Appeal Panel first sought and received confirmation that the 'other consultees' referred to in paragraph 4.3.17 were those represented by the joint appeal from Alzheimer's Society et al. The Appraisal Committee Chairman explained that it was the view of the Committee (and others) that there was a well established, distinct subgroup of people with agitation. The Alzheimer's Society's comments had been correct in seeking to delineate a difference in response to memantine between those with psychosis and those with agitation. However, the Alzheimer's Society representative disagreed with this interpretation of their comments. The Chairman proposed that the wording was changed better to reflect the impression of the Committee, namely that the manufacturer's categorising of people as behaviourally disturbed was neither specific enough nor consistent with the definition proposed by others in general.

3.10. The Appeal Panel concluded that the Committee had not been unfair or perverse.

3.11. The Panel referred point 13 to the Guidance Executive for further consideration.

**14. The guidance perversely prefers the cost effectiveness estimates of the Assessment Group to those of Lundbeck.**

3.12. The Panel noted that there was disagreement as to the assumptions made in the two models regarding cost effectiveness, but this did not evidence perversity on the part of the Appraisal Committee. The Panel also noted that, given that the clinical effectiveness test had not been passed, the cost effectiveness estimates used had no bearing on the ultimate recommendations in the FAD.

3.13. Appeal point 14 was therefore dismissed.

**15. The guidance perversely relies on inaccurately stated responder data.**

3.14. The inaccuracies identified in the FAD were acknowledged by the Committee, and have been referred back to the Guidance Executive (see appeal point 9 under Ground 1). The Panel noted that the material outcome of the guidance would not be affected, even if the responder data was inaccurately relied upon, as the clinical effectiveness test had not been passed.

3.15. Appeal point 15 was therefore dismissed.

**16. It is perverse for the FAD to suggest that memantine has been appraised in all its indications when only clinical data for moderately severe to severe Alzheimers Disease were taken into account.**

3.16. The Appraisal Committee acknowledged that this was a factual error, and the intention of the committee was to note that memantine had been considered within the moderately severe and severe disease groups only. Its use in patients with moderate disease had not been considered.

3.17. The Panel concluded that the wording of the FAD did not accurately reflect the intended meaning of the Committee.

3.18. The Panel referred this point to the Guidance Executive for their consideration.

**4. Ground 3: The Institute has exceeded its powers by failing to comply with the Transparency Directive**

4.1. The appellant contends that the Institute's appraisal constitutes a "measure" for the purposes of the Transparency Directive (Council Directive 89/105/EEC). The relevant test under Article 7 of the Transparency Directive is whether the Institute's guidance amounts to "a decision to exclude individual or categories of medicinal products from the coverage of [the UK's] national health insurance system (negative lists)". The appellant seeks to rely on paragraph 6.1 of the FAD in order to suggest that the appraisal goes beyond guidance so as to amount to "policy to be enforced". However, all guidance produced by the Institute is prefaced by the following statement:

***"This guidance is written in the following context***

*This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgment. This guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.”*

4.2. This preface accurately reflects the reality of the position. The FAD contains guidance, which is always subject to the clinical judgment of the individual practitioner, albeit it should always be taken into account.

4.3. The Appeal Panel concluded that the FAD does not constitute a ban on or “exclusion” of the use of drugs which it does not recommend (or recommends restrictively). It follows that the Transparency Directive does not apply to the FAD at all.

## **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.