NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Appraisal Consultation Document

Donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer’s Disease

The Department of Health and the National Assembly for Wales have asked the National Institute for Clinical Excellence (NICE or the Institute) to conduct an appraisal of donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer’s disease, and provide guidance on its use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted and the views put forward by the representatives nominated for this appraisal by professional organisations and patient/carer and service user organisations. The Committee has developed preliminary recommendations on the use of donepezil, rivastigmine, galantamine and memantine.

This document has been prepared for consultation with the formal consultees. It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk).

Note that this document does not constitute the Institute’s formal guidance on this technology. The recommendations made in Section 1 are preliminary and may change after consultation.

The process the Institute will follow after the consultation period is summarised below. For further details, see the Guide to the Technology Appraisal Process (this document is available on the Institute’s website, www.nice.org.uk).

- The Appraisal Committee will meet again to consider the original evidence and this Appraisal Consultation Document in the light of the views of the formal consultees.
- At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.
- After considering feedback from the consultation process, the Committee will prepare the Final Appraisal Determination (FAD) and submit it to the Institute.
- Subject to any appeal by consultees, the FAD may be used as the basis for the Institute’s guidance on the use of the appraised technology in the NHS in England and Wales.
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Details of membership of the Appraisal Committee are given in Appendix A and a list of the sources of evidence used in the preparation of this document is given in Appendix B.
1 **Appraisal Committee’s preliminary recommendations**

1.1 Donepezil, rivastigmine and galantamine are not recommended for use in the treatment of mild to moderate Alzheimer’s disease (AD).

1.2 Memantine is not recommended for the treatment of moderately severe to severe AD, except as part of ongoing or new clinical studies that are designed to generate robust and relevant data on long-term outcomes, disease progression, quality of life and costs.

1.3 People currently receiving donepezil, rivastigmine, galantamine and memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including at the conclusion of a clinical trial) until it is considered appropriate to stop.

2 **Clinical need and practice**

2.1 Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking and orientation. AD is the most common form of dementia. AD is a primary degenerative cerebral disease with characteristic neuropathological and neurochemical features.

2.2 AD is usually insidious in onset and develops slowly but steadily over a period of several years. AD predominantly affects the elderly. Progression is characterised by a deterioration in cognition (thinking, conceiving, reasoning), functional ability (activities of daily living), and behaviour and mood. Changes in one or more of these domains and their effects on the person and their carer’s wellbeing provide the basis for diagnosis, by assessing the severity
and progression of the condition. AD progresses from diagnosis to death in about 5-7 years.

2.3 People with AD lose the ability to carry out routine daily activities like dressing, undressing, toileting, travelling and handling money and, as a result, many of them require a high level of care. Often, this is provided by an elderly relative, whose own health and quality of life can be seriously affected by the burden of care provision. Behavioural changes in the person such as aggression are particularly disturbing for carers.

2.4 Non-cognitive symptoms in dementia include agitation, behavioural disturbances (for example, wandering or aggression), depression, delusions and hallucinations. These features are common, often difficult to treat, and are a much stronger predictor of both carer stress and entry into institutional care than cognitive impairment; they are therefore important targets for therapeutic intervention.

2.5 Several different methods are used to assess the severity of Alzheimer's disease. These include: the Clinician's Interview-based Impression of Change (CIBIC) and CIBIC-plus for global outcomes, the Progressive Deterioration Scale (PDS) for functional/quality of life scales and the 70 point, Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-cog) or the 30 point, Mini Mental State Examination (MMSE) for cognitive outcomes. MMSE score, for example, denotes the severity of cognitive impairment as follows:

- mild AD: MMSE 21 to 26
- moderate AD: MMSE 10 to 20
- moderately severe AD: MMSE 10 to 14
- severe AD: MMSE less than 10.
2.6 Population data (2002) for England and Wales show an estimated prevalence of 290,000 people with AD. On the basis of these figures a Primary Care Trust (PCT) with a population of 200,000 might expect to have approximately 1100 cases of AD. The incidence rate for AD in those over 65 years old has been estimated at 4.9 per 1000 person-years in the UK. The incidence rate appears to have been stable over the past two decades and is found to be related to age (rising with increasing age) and gender (women have higher risk than men). In people with AD, 50–64% are estimated to have mild to moderate disease while approximately 50% of patients have moderately severe to severe AD.

2.7 An estimated 22% of people with dementia live alone, 36% with carers and 29% in nursing homes. The total costs of care for people with dementia are estimated by the Audit Commission to be £6 billion for dementia, with half of this amount attributed to Health and Social Services.

2.8 People with dementia usually present to their general practitioner with memory problems, and an estimated 39% present to specialist clinics. The role of memory clinics has been further clarified by the National Service Framework for Older People. This states that referral to specialist mental health services should be considered for those with suspected dementia in a number of circumstances, not only for consideration of treatment but also, for example, if the diagnosis is uncertain, if certain behavioural and psychological symptoms are present, or if there are safety concerns with anti-dementia drugs, in accordance with local protocols.

3 The technologies

Acetylcholinesterase inhibitors: donepezil, rivastigmine, galantamine

3.1 Acetylcholinesterase (AChE) inhibitors raise the concentration of acetylcholine at sites of neurotransmission. Since the original NICE guidance
of 2001\(^1\) the number of prescribed defined daily doses for the AChE inhibitors, especially donepezil, has increased markedly. Substantial regional variation in spending is seen across Strategic Health Authorities in England and Wales.

3.2 Donepezil (Aricept\textregistered{}, Eisai) is a specific and reversible inhibitor of AChE licensed in the UK at a dose of 5 mg/day and 10 mg/day for the symptomatic treatment of mild to moderately severe Alzheimer’s dementia. Prices are £63.54 for 28 tablets of 5 mg and £89.06 for 28 tablets of 10 mg (excluding VAT; *British National Formulary* [BNF] 48th edition and January 2005 communication from Eisai on price adjustment). This equates to £828.30 and £1160.96 per year of treatment respectively. Costs may vary in different settings because of negotiated procurement discounts. In 2003, 77\% of prescriptions for AChE inhibitors were for donepezil.

3.3 Rivastigmine (Exelon\textregistered{}, Novartis) is an acetyl- and butyrylcholinesterase licensed in the UK for the treatment of mild to moderately severe AD. The usual dose range is 3–6 mg twice daily, with a maximum of 6 mg twice daily (*BNF 48th edition*). Prices are £68.04 for 56 capsules of 1.5 mg, 3 mg, 4.5 mg and 6 mg (excluding VAT; *BNF 48th edition*). This equates to approximately £886.95 per year of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.4 Galantamine (Reminyl\textregistered{}, Shire) is a selective, competitive and reversible inhibitor of AChE licensed in the UK for symptomatic treatment of mild to moderately severe dementia of the AD type. Galantamine also appears to enhance the activity of both pre- and post-synaptic nicotinic acetylcholine receptors, but the clinical relevance of this is unclear. The maintenance dose

is between 8 and 12 mg twice daily (BNF 48th edition). Prices are £68.32 for 56 tablets of 8 mg and £84.00 for 56 tablets of 12 mg (excluding VAT; BNF 48th edition). This equates to approximately £890.60 and £1095 per year of treatment, respectively. Costs may vary in different settings because of negotiated procurement discounts.

3.5 Side effects of donepezil, rivastigmine and galantamine are typically related to the gastrointestinal tract. These side effects are usually produced acutely, and tend to be dose related. For full details of side effects and contraindications, see the Summary of Product Characteristics.

Memantine

3.6 Memantine (Ebixa®, Lundbeck) is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. Memantine is licensed for the treatment of people with moderately severe to severe AD. The recommended maintenance dose is 10 mg twice daily. Prices are £69.01 for 56 tablets of 10 mg (excluding VAT; BNF 48th edition and January 2005 communication of Lundbeck on price adjustment). This equates to approximately £899.54 per year of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.7 The mild to moderately severe side effects associated with the use of memantine include hallucinations, dizziness, confusion, headache and tiredness. For full details of side effects and contraindications, see the Summary of Product Characteristics.

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources (see Appendix B).
4.1 Clinical effectiveness

Mild to moderate AD

4.1.1 The quality of the reporting and methodology of the included published randomised controlled trials (RCTs) of the cholinesterase inhibitors was generally mixed. The Assessment Group suspected selection bias, measurement bias and attrition bias in a number of the reviewed studies.

4.1.2 Donepezil

4.1.2.1 Thirteen RCTs (aggregate number of people randomised 4200), one unpublished RCT and two systematic reviews met the inclusion criteria set by the Assessment Group for the systematic review of clinical effectiveness of donepezil (the original guidance included five RCTs, four studies from manufacturers and three systematic reviews). Three of the new trials followed participants for a period longer than 6 months.

4.1.2.2 Six RCTs reviewed by the Assessment Group showed, using the ADAS-cog scale, that donepezil appears to confer a statistically significant benefit to participants' cognition when compared with placebo. Higher doses of donepezil were associated with increasing benefit. Three RCTs with a duration of 12 to 24 weeks contained data in a form that could be combined by the Assessment Group in a meta-analysis. A weighted mean difference of −2.51 (95% confidence interval [CI] −3.26 to −1.76) in terms of a change from baseline was found for the 5 mg daily dose and a weighted mean difference of −3.01 (95% CI −3.91 to −2.10) was found for the 10 mg daily dose when compared with placebo. An analysis based on the trial of 24 weeks duration produced a mean difference in ADAS-cog change from baseline at 24 weeks of −2.88 (95% CI −4.27 to −1.49).

4.1.2.3 Eight RCTs showed trends towards improved MMSE scores in the donepezil-treated groups when compared with placebo. The AD2000
study differs from the trials sponsored by the drug industry in that the participants were typical UK patients, referred from memory clinics and managed by local doctors who had minimum study-related tasks. Participants were treated in a placebo-controlled randomised trial with indefinitely long follow-up at doses of 5 mg or 10 mg donepezil a day. No statistically significant effect of donepezil was seen on the primary outcomes of the study (entry into institutional care and progression of disability). Cognition, measured by MMSE, was included as a secondary outcome. Over the 2-year study period the MMSE scores of the donepezil group were an average of 0.8 points higher than those of the placebo group (95% CI 0.5 to 1.2, \( p < 0.0001 \)). AD2000 was not included in the Assessment Group’s meta-analysis of effect on MMSE for donepezil.

4.1.2.4 Seven RCTs (aggregate number of people randomised 2500) assessed the effect of donepezil on global outcomes compared with placebo using the CGIC or CIBIC-plus. Participants using donepezil showed a significantly greater change in CGIC/CIBIC-plus scores from baseline when compared with placebo.

4.1.2.5 Studies reporting on the short-term effects of donepezil using a variety of measures of activities of daily living generally found better, or less deterioration in, functional ability than placebo, although these findings were not statistically significant in all trials. No significant difference was apparent between donepezil and placebo in rates of institutionalisation in the AD2000 trial (9% donepezil versus 14% placebo at 1 year, \( p = 0.15 \); 42% versus 44%, respectively, at 3 years, \( p = 0.4 \)). Furthermore, similar proportions of participants had progression of disability (13% donepezil versus 19% placebo at 1 year, \( p = 0.3 \); 55% versus 53%, respectively, at 3 years, \( p = 0.9 \)).

4.1.2.6 Quality of life estimates associated with the use of donepezil showed varied results, and only three studies reported on this outcome. Over the
three studies, the impact of donepezil derived from this set of health measurements is unclear. Moreover, all trials used non-validated scales for dementia. The respective results showed improvements, no change and worsening of quality of life, with the impact of the dose used for donepezil being unclear.

4.1.2.7 Behavioural symptoms were measured using the neuropsychiatric inventory (NPI) in four RCTs of donepezil. The results varied but generally suggested that donepezil may have some effect in improving or limiting further deterioration on the NPI scale compared with placebo, at least in the short term.

4.1.2.8 Adverse events were more frequently recorded in participants receiving donepezil than in those on placebo, and higher doses of donepezil increased the frequency of adverse events. Withdrawals due to adverse events were associated with similar losses in the groups on low-dose donepezil and those on placebo. However, higher doses of donepezil tended to lead to more withdrawals.

4.1.2.9 The manufacturer’s submission included a 24-week RCT that evaluated the safety and efficacy of donepezil in people with moderately severe AD (baseline MMSE score 5–17) and compared them with placebo. People receiving donepezil scored statistically significantly better on global, cognitive, functional and behavioural outcomes. A number of open-label and observational studies were also included in the manufacturer’s submission. The effect size of donepezil on cognitive and global outcomes in these studies was similar to those recorded by other RCTs. The use of donepezil also appeared to show a benefit on outcomes such as ‘delayed time to nursing home placement’ and improvements in social behaviour (assessed by the care giver diary) when valued in the context of these observational studies.
4.1.2.10 The manufacturer's submission and the Assessment Report included a study that aimed to establish the effect of continuation of treatment with donepezil for 153 people who had not shown a response ('no apparent clinical benefit') after 24 weeks of open-label donepezil treatment. Randomisation of those who showed no response and who were subsequently treated for 12 weeks (double-blind) with donepezil (10 mg/day) was associated with a significantly higher MMSE score and a significantly lower NPI score than those receiving placebo.

4.1.2.11 In summary, evidence from studies using cognitive and global outcome measurement scales suggests that donepezil appears to be beneficial in treating AD. The effect of donepezil on functional outcomes, quality of life and behavioural symptoms in AD is less conclusive. The AD2000 trial substantiates these general findings but suggests a lower effect size on cognition than was found in the Assessment Group meta-analysis.

4.1.3 Rivastigmine

4.1.3.1 Four published RCTs (aggregate number of people randomised 1940), two unpublished RCTs (aggregate number of people randomised 1380) and three systematic reviews met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of rivastigmine. All published comparisons were versus placebo with trials reporting doses of between 1 and 12 mg/day and durations of 26 weeks or less. The original NICE guidance was based on three systematic reviews, five RCTs and two unpublished studies from manufacturers.

4.1.3.2 Four RCTs reviewed by the Assessment Group showed that the higher dose of rivastigmine (6–12 mg/day, mean dose approximately 10 mg/day) appeared to confer a statistically significant benefit to participants when compared with placebo, as measured using the ADAS-cog scale. One RCT found no significant differences. A meta-analysis by the Assessment
Group of two RCTs, both with a duration of 26 weeks, was associated with a weighted mean difference of $-3.08$ (95% CI $-3.78$, $-2.38$) for 6–12 mg of rivastigmine per day when compared with placebo. Statistically significant heterogeneity was found when pooling the two studies for meta-analysis, which led the Assessment Group to conclude that the statistically significant treatment effect seen for rivastigmine (6–12mg) in the fixed-effect model should be treated with caution.

4.1.3.3 Three RCTs showed significantly better MMSE scores in the groups treated with rivastigmine in the higher dose regimen compared with placebo. None of the studies using a low-dose regimen found statistically significant differences for rivastigmine versus placebo.

4.1.3.4 Four RCTs assessed the effect of rivastigmine compared with placebo on the CIBIC-plus scale. In the two published RCTs participants demonstrated mean changes from baseline that were statistically significantly better with rivastigmine in the high-dose regimen only. The percentage of improvers or responders on the CIBIC-plus was also calculated in the two published studies. Clinical improvement was defined as a score of one, two or three on the CIBIC-plus scale. Between the two trials, 16% to 20% of participants treated with placebo were judged to have responded versus 30% to 57% for users of rivastigmine. A statistically significant difference was found for the high-dose regimen only.

4.1.3.5 Generally, participants treated with 6–12 mg/day rivastigmine demonstrated statistically significant better functional outcomes than participants on placebo. One (700 people randomised) of the four studies (aggregate number of people randomised 2800) using the PDS showed that there was no statistically significant difference from placebo for either the low- or high-dose regimen when compared with placebo.
4.1.3.6 The Nurses Observation Scale for Geriatric Participants (NOSGER) was used in two rivastigmine RCTs. No statistically significant benefit was demonstrated on measures of mood and behaviour in the groups treated with rivastigmine compared with the placebo groups.

4.1.3.7 Levels of nausea and vomiting were particularly high among participants treated with the higher dose of rivastigmine. Withdrawals due to adverse events were reported in all studies and these varied considerably. The manufacturer noted that better adherence to the up-titration schedule should improve gastrointestinal tolerability.

4.1.3.8 A number of open-label and observational studies were included in the manufacturer’s submission. The duration of these trials was between 26 weeks and 5 years. The effect size of rivastigmine on cognitive and behavioural outcomes was similar to those seen in the RCTs. Other open-label and observational studies, and experience with rivastigmine in a ‘real-world’ setting, appeared to show some benefit in outcomes such as ‘delayed time to nursing home placement’ and caregiver burden.

4.1.3.9 The manufacturer’s submission included a prospective, open-label study that evaluated the efficacy and safety/tolerability of rivastigmine in people who had failed to benefit from treatment with donepezil (because of a lack of efficacy [80%] or tolerability [11%], or both [9%]). After 26 weeks 56.2% of patients had responded to rivastigmine (defined as improvement/stabilisation of symptoms using the CGIC).

4.1.3.10 In summary, a range of fixed and flexible dosing regimes of rivastigmine were investigated across studies, which makes interpretation of the evidence more difficult. Evidence from studies using cognitive and global outcome measurement scales suggests that rivastigmine may be beneficial in AD at higher doses (6–12 mg). Evidence for an effect on functional outcomes was less conclusive and no benefit of rivastigmine on
measures of behaviour and mood was reported. Side effects of the use of rivastigmine were considerable at higher doses and led to withdrawals in studies. The results of the meta-analysis on cognition should be treated with caution because of statistically significant heterogeneity in the fixed-effect model.

4.1.4 Galantamine

4.1.4.1 Six published RCTs, one unpublished RCT (aggregate number of people randomised 4300) and one systematic review met the inclusion criteria set by the Assessment Group for the systematic review of clinical effectiveness of galantamine. All comparisons were versus placebo, with trials reporting dosing regimens between 8 mg/day and 36 mg/day and durations of 3 to 6 months. One systematic review, three RCTs and three studies from manufacturers were identified in the literature at the time of the original appraisal.

4.1.4.2 All six published RCTs and the unpublished RCT assessed the clinical effectiveness of galantamine compared with placebo using the ADAS-cog scale. In all studies galantamine appeared to confer a statistically significant benefit to participants when compared with placebo. The benefit varied depending on the dose of galantamine. Three RCTs of treatment with galantamine at a dose of 24 mg were combined by the Assessment Group in a meta-analysis. The fixed-effect model showed a weighted mean difference of –3.37 (95% CI –4.11 to –2.63) favouring galantamine over placebo.

4.1.4.3 Six RCTs assessed the effect of galantamine compared with placebo on the CIBIC-plus. They showed that in individual studies more participants on galantamine improved than on placebo (0% to 6.5% more), whereas more participants on placebo than on galantamine deteriorated (4% to 18% more). When the studies were pooled by the Assessment Group
(aggregate number of people randomised 3300) no statistical significance was noted between treatment groups and placebo.

4.1.4.4 Participants receiving galantamine appeared to undergo statistically significantly less deterioration than those on placebo for doses between 16 mg/day and 32 mg/day on scales that measure activities of daily living.

4.1.4.5 In one trial higher doses of galantamine (16 mg/day or over) were associated with a statistically significant slowing in the deterioration of participants’ condition on NPI compared with placebo. In two trials the slowing of deterioration was not statistically significantly different between treatment and control groups.

4.1.4.6 Across RCTs, between 2% and 27% more participants on galantamine suffered from an adverse event compared with placebo. Withdrawals due to adverse events were associated with a loss of between 6% and 44% of galantamine participants, with differences following a dose–response relationship.

4.1.4.7 The manufacturer’s submission presented a pooled analysis of two 6-month RCTs in people with mild to moderate AD that suggested a statistically significant decrease in the overall mean amount of time care givers spent assisting people with activities of daily living. The decrease was 32 minutes/day for patients treated with galantamine at a dose of 24 mg/day when compared with placebo. A number of open-label studies included in the manufacturer’s submission suggested a slightly reduced long-term decline in the cognition of people treated with galantamine.

4.1.4.8 In 6-week follow-on studies of two RCTs (aggregate number of people randomised 570) included in the manufacturer’s submission, patients who were switched from galantamine to placebo experienced a greater decline on measures of cognition than those who remained on galantamine. This
difference reached statistical significance only in the study where no randomisation was involved in deciding whose treatment should be stopped (number of participants 500).

4.1.4.9 Evidence from studies using cognitive and functional outcome measurement scales suggest that galantamine may be beneficial in AD. Improved benefits in cognition tended to be related to higher doses. Improvements in measurements of function were also demonstrated at higher doses. On global outcome measures, individual studies showed higher proportions of participants improving with galantamine, but this was not reflected in the meta-analysis. In some studies considerably more participants withdrew because of adverse events.

4.1.5 Head-to-head comparisons

4.1.5.1 Three RCTs met the inclusion criteria for the review by the Assessment Group. Two compared donepezil with rivastigmine and one compared donepezil with galantamine. The Assessment Group regarded the quality of the studies as generally poor. The manufacturer’s submission for galantamine included a study comparing galantamine with donepezil, but this study was excluded by the Assessment Group because the study did not describe its population as mild to moderate AD by any definition and the MMSE scores fell outside the range of 10–26.

4.1.5.2 When directly compared with donepezil, treatment with rivastigmine showed no statistically significant differences on measures of cognition or function. Rates of adverse events tended to be higher in participants in the rivastigmine groups but the manufacturer’s submission for rivastigmine argued that slower titration is recommended for clinical practice than was used in this trial.
4.1.5.3 In the comparison between galantamine and donepezil that was sponsored by the manufacturer of donepezil, participants on galantamine showed improvement on measures of cognition and function but the improvement in participants on donepezil was greater. However, in the comparison that was funded by the manufacturer of galantamine this effect seemed to be reversed and it appeared that galantamine exerted a more sustained effect than donepezil.

Modestly-severe to severe AD

4.1.6 Memantine

4.1.6.1 Two RCTs (aggregate number of people randomised 650) met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of memantine. Both studies reported on participants with moderately severe to severe AD, as measured by the MMSE, and compared 20 mg/day of memantine with placebo; one study made the comparison over a period of 24 weeks and the other over 28 weeks. In the first study participants were included on the basis that they had already been receiving donepezil for more than 6 months before entering the trial, and had been at a stable dose (5–10 mg/day) for at least 3 months. These participants were maintained on stable donepezil for the duration of the study. The quality of reporting and methodology of the two trials was generally good.

4.1.6.2 People treated with memantine in both studies showed statistically significantly less deterioration of cognitive function measured by the Severe Impairment Battery (SIB), but deterioration as measured by the MMSE was not statistically significantly different between the treatment and control groups. Memantine was statistically significantly more effective than control in improving global function as measured by CIBIC-plus. Both trials used the Alzheimer’s Disease Cooperative Study – Activities of Daily
Living 19 (ADCS-ADL19/sev) scale (which focuses on the assessment of later stages of dementia) to measure functional outcome, and reported statistically significantly less deterioration following the use of memantine compared with control. Participants receiving memantine who were also on a course of donepezil had a statistically significantly lower NPI score for behavioural symptoms compared with the control group of donepezil alone. In the separate trial of memantine alone (250 people randomised), however, no statistically significant difference compared with placebo was observed. The frequency of adverse effects was similar for both the memantine and control groups. Despite this, the rate of withdrawal due to adverse events was relatively high in the memantine group.

4.1.6.3 During the course of the review and after the Assessment Report had been produced, the manufacturer of memantine provided summary results of a further trial of memantine against placebo, the results of which are commercial-in-confidence. In other material provided by the manufacturer, caregivers, as assessed by the Resource Utilization in Dementia score, were estimated to spend less time with participants receiving memantine (difference between treatment groups, 45.8 hours per month; 95% CI, 10.37 to 81.27; p = 0.01). This amounts to between 20 minutes and 2 hours 45 minutes per day, with a most probable difference of 1 hour 30 minutes a day. The results of an open-label extension study of one of the pivotal trials suggest that effects of memantine can be sustained over a period of 12 months.

4.1.6.4 Memantine showed beneficial effects in participants with moderately severe to severe AD in terms of functional and global measurements, where participants in the treatment arms showed less deterioration than those in the placebo arm. The effect of memantine on cognitive outcome measurements was also favourable, although this was not always statistically significant (notably on MMSE). On measures of behaviour and
mood memantine was beneficial only in the groups already receiving donepezil.

4.2 Cost effectiveness

Mild to moderate AD

4.2.1 Twenty-one published economic evaluations of the three AChE inhibitors and memantine were available to the Appraisal Committee. All four manufacturers also submitted their own economic evaluations. The Assessment Group re-ran each of the manufacturer’s economic models using their preferred assumptions and also performed their own economic evaluation of the three AChE inhibitors, but not of memantine.

4.2.2 Donepezil

4.2.2.1 Eleven economic evaluations for donepezil were found. Three related to the UK. One of the eleven studies was of treatment for people with mild AD; the other ten were of mild to moderate AD. In five (of 11) studies donepezil was found to be cost saving.

4.2.2.2 Of the three UK-based studies, an early independent study, based on drug costs only, estimated a cost per quality-adjusted life-year gained (CQG) for the 5 mg dose per day of £21,000 (2-year model) to £86,000 (10-year model) for a gain of 0.08 QALYs per person, and of £35,000 to £139,000 when the QALY gain was only 0.05.

4.2.2.3 In a UK study associated with the manufacturer, the cost of gaining an additional year in a non-severe state was measured. The cost was estimated to have ranged from £4500 to £7000, depending on dose and starting point (mild or moderate AD).

4.2.2.4 The AD2000 study found that the drug was not cost effective, mainly because there were no apparent benefits of the drug in delaying
progression of the disease or of time to institutionalisation. The authors doubted that the drug would prove to be cost effective; even if changes in carer costs were included, the drug would not prove to be cost effective.

4.2.2.5 The manufacturer’s model used a transition state modelling approach in which disease progression is modelled across different levels of AD severity to estimate the incremental cost effectiveness of donepezil compared with placebo. Transition probabilities were derived from trial data, with the drug efficacy rate persisting for the initial 12-month cycle of the model. For the remainder of the 5-year model the transition probabilities for the treated group were proportional to those of the placebo group. Cost estimates were taken from the literature in which they were calculated for different severity levels of AD by MMSE score. The submission reported that for the base case of people with a MMSE score of 13–26, treatment with donepezil 10 mg daily resulted in an estimated £1200 per year outside of the severe AD state. Inclusion of the people with a MMSE of 10–12 increased this to £4000 per year outside of the severe state. The manufacturer’s model allowed for estimates of CQG to be calculated but did not report results in terms of CQG either in the base case analysis or in the sensitivity analyses.

4.2.2.6 The Assessment Group noted that the use of cognitive function alone to model disease progression is likely to misrepresent this disease progression over time. Where the Assessment Group incorporated alternative cost estimates as well as an increased mortality risk and a half-cycle correction, the manufacturer’s model estimated an incremental cost effectiveness of £14,000 per year outside of the severe state. When the Assessment Group used an incremental utility of 0.3 to represent the transition between severe and non-severe AD, this incremental cost effectiveness translated to a CQG estimated to be £45,000.
4.2.3 Rivastigmine

4.2.3.1 Five economic evaluations for rivastigmine were found, one of them in abstract form only. Two related to the UK. All were of people with mild to moderate AD. Four, including all three industry-associated studies, were found to be cost saving.

4.2.3.2 Of the two UK-based studies, an independent study estimated a range of incremental cost-effectiveness ratios; the estimates varied depending on the time duration used by the models, which ranged from 1 year (more cost effective) to 5 years (less cost effective) and on the number of QALYs gained (0.05 or 0.08). These models resulted in CQG estimates ranging from £16,000 to £46,000. Separate estimates were provided when non-drug treatment costs were included, and these ranged from £15,000 to £89,000.

4.2.3.3 In a study supported by the manufacturer, estimated cost savings (but not including the cost of rivastigmine) after 2 years were £1300 for people with mild AD and £800 for those with moderate AD.

4.2.3.4 The manufacturer’s submission detailed a 5-year model that combines data on clinical pathways from a trial, a statistical model of the natural history of AD using MMSE, and a mapping process estimating utility values for AD based on MMSE scores. Cost estimates in the model were related to probabilities of institutional care as a function of MMSE. The CQG of rivastigmine (combined doses) plus usual care versus usual care alone was estimated to be £25,000.

4.2.3.5 The Assessment Group expressed specific concerns about the method used to derive a QALY value in the manufacturer’s model, especially where it is related to the MMSE. Apart from incorporating alternative cost estimates in the manufacturer’s model, the Assessment Group also halved
the proposed utility benefit that would result from a one unit change in MMSE score. These adjustments led to a CQG estimate of £46,000.

4.2.4 Galantamine

4.2.4.1 Five economic evaluations for galantamine were found. One related to the UK. All published economic evaluations on galantamine used the same methodology for modelling disease progression – the Assessment of Health Economics in Alzheimer’s Disease (AHEAD) model.

4.2.4.2 All studies estimated that galantamine was cost saving for moderate AD. For mild AD, four studies showed galantamine to be cost saving, and the fifth, a UK study, was associated with a CQG for galantamine of £9000.

4.2.4.3 The manufacturer’s submission also presented a cost-effectiveness analysis for galantamine using the AHEAD modelling framework. The AHEAD model rests on the concept of need for full-time care (FTC), and simulates the experience of a cohort of patients across three possible health states: pre-full-time care (pre-FTC), FTC and death. Following an initial treatment period of 6 months, patients’ experiences are simulated over a time horizon of 10 years. The model uses patient characteristics at a given point in time to estimate the likelihood of disease progression over time to a level at which FTC is required. Parameters used in the predictive risk/hazard equations for FTC and death in the AHEAD model include age, presence of extrapyramidal symptoms (EPS), presence of psychotic symptoms, age at onset, duration of illness and a cognitive score as measured by the modified MMSE (mMMS). The authors did not present details of the findings from clinical trials on these outcome measures. Cost estimates in the model were taken from published UK data. Health state utility data were taken from a cross-sectional study of care givers of AD patients in the US, based on the Health Utility Index Mark 2 questionnaire and stratified by disease severity. For patients treated with galantamine
24 mg/day the model estimated a delay to FTC of 3.02 months, which equates to 0.07 QALYs and a CQG of £10,000. The model predicted net savings for people with moderate AD (MMSE < 18) and for those who showed response to treatment after 6 months. No probabilistic sensitivity analyses were reported.

4.2.4.4 Although the Assessment Group noted that the structure of the model involves only two health states and that this may be seen as a crude reflection of the natural history of AD, they accepted that these states can be regarded as those relevant to this Appraisal. The Assessment Group expressed concerns about the fact that the risk equations had been derived from an observational study and that there was a need to transform the ADAS-cog or MMSE scores to reflect an mMMS score, but nevertheless recognised that it was the best available way to illustrate potential progression of AD over time. The Assessment Group applied the costs and time frame (5 years) used in their own modelling to the AHEAD model, which resulted in an estimated CQG of £49,000.

4.2.5 Assessment Group model

4.2.5.1 The Assessment Group used the framework of the AHEAD model in order to illustrate a simple model of disease progression that allows for all three AChE inhibitors to be modelled using the same framework. The model estimates cost effectiveness of AChE inhibitors plus usual care versus usual care alone in a UK context from the perspective of a third party payer. Cohorts of 1000 people with mild to moderately severe AD were modelled in a Markov disease progression model over a time horizon of 5 years. The predictive risk equation for FTC of the AHEAD model was used unchanged, while the risk equation for mortality of AHEAD was substituted for an annual mortality rate of 11.2% for all patients.
4.2.5.2 Effectiveness data for the three AChE inhibitors were based on the Assessment Group’s meta-analyses of trials reporting ADAS-cog. Costs for the pre-FTC and FTC health states were estimated after the Group reviewed the literature, and results were combined from numerous sources. The Assessment Group assumed that only 70% of costs of FTC in an institutional setting would be met by the NHS and thus excluded the 30% of these costs that were met by the patients. In the absence of other data, the Assessment Group used the health state utility data from the US cross-sectional study of care givers of people with AD. A utility value of 0.60 was assumed for the pre-FTC health state and 0.34 for the FTC health state, resulting in a difference of 0.26 between health states. Parameter uncertainty was considered as part of the probabilistic modelling process with distributions around point estimates allowing variation within the main analysis (that is age, ADAS-cog score, AD duration, effectiveness, monitoring costs, costs for pre-FTC and FTC, and health utilities).

4.2.5.3 The results of the Assessment Group model were presented both deterministically and probabilistically. The difference in time spent in FTC over 5 years ranged from 1.43 to 1.60 years, and QALYs gained ranged from 0.042 to 0.048. The resulting base case CQGs were £94,000 for donepezil (10 mg daily), £64,000 for rivastigmine (6–12 mg daily) and £71,000 for galantamine (24 mg daily). The results were sensitive to a range of alternative inputs, particularly in relation to the effectiveness of the drugs, health state utility and cost inputs for longer-term care. Limitations of the modelling approach were identified by the Assessment Group.

4.2.6 Extra analyses undertaken by NICE’s secretariat

4.2.6.1 In addition to the economic analyses carried out by the Assessment Group and the manufacturers, the NICE secretariat conducted further economic
analyses. The Committee requested that these analyses incorporate an assessment of the impact on the Assessment Group model of using alternative cost estimates, extra benefits from using the AChE inhibitors and sensitivity analyses on mortality and psychotic symptoms. Additionally, the alternative cost estimates were to include a scenario in which 100% of the costs of institutional care would be met by the NHS. The extra benefits also included those benefits of the AChE inhibitors that should be accrued to patients who, at the end of the time horizon of the model, would not have had the capacity to benefit – that is, patients who died in pre-FTC or who were in pre-FTC at the end of the model and who were still using an AChE inhibitor. An extra benefit was also given to those in the 6-month trial period on an AChE inhibitor and to whom the Assessment Group model assigned drug and monitoring costs. Moreover, it was also assumed, on the basis of a submitted relationship between cognition (MMSE) and utility, that the benefit for the pre-FTC health state should lie at 0.69 instead of 0.60, resulting in a difference of 0.35 between pre-FTC and FTC health states. Separate analyses were also undertaken that estimated the impact of including carer benefits and of varying the starting severities of the patient cohorts using the Assessment Group model.

4.2.6.2 An augmented base case for the Assessment Group model was formulated that included alternative cost estimates and all extra health benefits mentioned in 4.2.6.1, as well as the increase in utility for pre-FTC. When the cost component of the augmented base case was compared with the cost estimates of the Assessment Group base case there was no substantial difference between the two. When only the cost estimates were altered to reflect the assumption that 100% of institutional costs are met by the NHS, the resulting CQG estimates were £88,000, £54,000 and £61,000 for donepezil, rivastigmine and galantamine, respectively. The complete augmented base case resulted in an estimated CQG of £52,000,
£32,000 and £38,000 for donepezil, rivastigmine and galantamine, respectively. The donepezil figure does not include the 7% price reduction announced in January 2004 (communication Eisai), but if included the CQG would have decreased to £48,000.

4.2.6.3 There is very little quantitative evidence related to carer utilities. The inclusion of different assumptions on the magnitude of changes in carer utility was associated with marginally lower estimates of CQGs. Modelling of cohorts of people with various levels of severity of AD resulted in lower CQGs for milder AD (£44,000 for donepezil in cohort with MMSE 24) and higher CQGs for more severe AD (£63,000 for donepezil in cohort with MMSE 17).

4.2.6.4 In the one-way sensitivity analysis on mortality on the augmented base case, a change in annual mortality rate only marginally affected CQG estimates. A range of estimates of the prevalence of psychotic symptoms were used to assess the impact on the CQG estimates. On its own, changing the estimates of effects of therapy on psychotic symptoms made no substantial difference to the CQG for the augmented base case. However, when the highest estimate of prevalence of psychotic symptoms (50%) was combined with an assumed effect of treatment (20% reduction), the resulting estimated CQG for donepezil was £37,000.

**Modestly severe to severe AD**

4.2.7 Memantine

4.2.7.1 Five economic evaluations of people with moderately severe to severe AD for memantine were found; three were in abstract or poster form, and the other two were in press. One of these related to the UK. All were found to be cost saving.
4.2.7.2 In the model submitted by the manufacturer, disease states were
described by severity, dependency, whether people are in institutional care
or not, and death. The people in the model made transitions between the
states. The time horizon was 2 years. Against placebo, memantine was
estimated to be cost saving in the moderately severe to severe group.
Subgroup analysis showed that memantine was cost saving in people who
could live independently and in moderately severe people who were
dependent. For people with severe AD who were dependent, the QALY
gain was estimated to be £4200. In combination with donepezil,
memantine was estimated to be cost saving against donepezil alone.

4.2.7.3 The Assessment Group ran the model using a similar set of assumptions
to those used in its own model, and arrived at a CQG of between £37,000
and £53,000. Further changes to transition probabilities that were thought
to be too optimistic in relation to the available trial evidence for, and costs
of care associated with, memantine raised the estimated CQG
substantially above £50,000.

4.2.7.4 The Assessment Group did not produce its own model for memantine for
moderately severe to severe AD.

4.2.7.5 The manufacturer submitted a second economic evaluation, which
compared the use of memantine in combination with donepezil against
donepezil monotherapy. The result suggested that the combination of the
two drugs was less costly and more effective than the use of donepezil
alone.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost
effectiveness of AChE inhibitors (donepezil, rivastigmine and galantamine)
and memantine, having considered evidence on the nature of the condition
and the value placed by users on the benefits of these drugs by people with
Alzheimer’s disease, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

**Acetylcholinesterase inhibitors**

4.3.2 The Committee heard that since its original guidance, the clinical evidence base for AChE inhibitors has matured and that it demonstrates a consistent gain on cognitive and global scales compared with placebo in mild to moderate AD. However, the Committee also noted that these gains were small on many of the measures of effect. The Committee also learned that there is little positive randomised evidence available on the long-term gain of the AChE inhibitors. Thus the Committee observed that the RCT evidence on outcomes of importance to patients and carers, such as quality of life and time to institutionalisation, was limited and largely inconclusive.

4.3.3 The Committee, having regarded the range of effectiveness estimates for the AChE inhibitors, both individually and collectively, concluded that it would not be reasonable to make a distinction in their recommendations between the effectiveness of the three drugs. The Committee further noted the inconclusive results from direct comparisons between the AChE inhibitors.

4.3.4 The Committee carefully examined the cost-effectiveness assessments provided. The Committee noted the substantial differences in CQG estimates resulting from the manufacturers’ models and those of the Assessment Group. The manufacturers’ cost-effectiveness calculations were noted to have a number of shortcomings, such as optimistic assumptions on costs and utilities. The Committee considered that the Assessment Group’s model was the most useful for decision-making purposes because it focused on the outcomes of most importance in AD, used more realistic inputs on costs and allowed for all AChE inhibitors to be modelled within a common framework.
4.3.5 Both the Assessment Group’s model and the manufacturers’ models, when re-evaluated using the Assessment Group’s assumptions on costs and utilities, put the AChE inhibitors outside the range of cost effectiveness that might be considered appropriate for the NHS.

4.3.6 However, the Committee heard from experts that the benefits of the drugs, although small as represented by changes on scales for cognition, were clinically relevant. Furthermore, a minority of people with AD were observed to benefit significantly from the AChE inhibitors. The experts also emphasised the effect of AChE inhibitors on behavioural symptoms in AD. The Committee heard that because the use of some antipsychotics in treating behavioural symptoms with AD is no longer recommended it could be appropriate to use AChE inhibitors for this indication. The experts further pointed to the benefits to carers of any amelioration of the cognition, function and behavioural symptoms of people with AD.

4.3.7 The Committee therefore considered different possible approaches to estimating the cost effectiveness of the AChE inhibitors and discussed a range of considerations that could change the cost effectiveness of AChE inhibitors from those of the Assessment Group’s base case estimates. These considerations included: alternative cost estimates; assuming a direct relationship between cognition and utility and thus imputing a higher utility for pre-FTC; benefits that accrue to individuals who do not reach FTC in the time-frame of the model; benefits to individuals who die before reaching FTC; benefits that accrue to carers; benefits arising from the amelioration of behavioural disturbance; and the effect of different mortality assumptions. However, on reviewing the additional analyses that had been undertaken, the Committee agreed that none of these considerations individually, or even when taken together, would put the AChE inhibitors within the range of cost effectiveness that might be considered appropriate for the NHS.
4.3.8 The Committee, having concluded that the incorporation of carer benefits in the economic modelling in the form of utilities was appropriate, also discussed whether carer costs should be included in the economic model. The Committee heard that, when the effect on carers is to be considered in an economic evaluation, it should only be considered from the point of view of either carer benefits, in the form of improvements in quality of life (utilities), or carer costs in the form of some (monetary) valuation of the opportunity costs of caring, but not both. The Committee also noted that the relevant NICE guidance on performing economic evaluations states that costs related to NHS and PSS resources that are required to achieve clinical and health-related benefits are the only appropriate ones to include.

4.3.9 The Committee considered the potentially greater need for the AChE inhibitors given the non-availability of certain antipsychotics for the behavioural symptoms associated with dementia; however, it also heard that AChE inhibitors are not necessarily the only other option for these people. The evidence for their additional effectiveness in this respect was not sufficient to alter the overall conclusions.

4.3.10 Additionally, the Committee noted a number of considerations which suggest that the cost effectiveness of the AChE inhibitors might be even less favourable than the estimates originally indicated in the Assessment Report. Thus the Committee noted that the results from the AD2000 trial were not included in the Assessment Group’s meta-analysis of the effect of donepezil on ADAS-cog, the result of which was subsequently used in the economic modelling. Furthermore, the results from the studies that did contribute to the calculation would have been less favourable towards the AChE inhibitors if they had been limited to their longer term (24 week) findings being incorporated in the meta-analyses.

4.3.11 The Committee heard that including the costs of institutional care that are met by patients (30%) was not justified when considering relevant Guidance on...
methods to be used in submissions to NICE. Although the Guidance does recommend the inclusion of any element of the NHS and PSS budgets contributed by patients, the Committee heard that the contributions that people with AD make towards institutional care are not part of these budgets. The Committee noted that by removing this element, the CQG in the augmented base case would increase to £54,000 for donepezil, and to £40,000 and £45,000 for rivastigmine and galantamine, respectively.

4.3.12 The differences in the cost-effectiveness estimates of the drugs in the augmented base case were not considered to reflect significant differences in the drugs’ effectiveness; and with the recent convergence in the price of the drugs, it was not considered reasonable to differentiate between them on the basis of their cost effectiveness.

4.3.13 The Committee considered whether there were any subgroups for whom the AChE inhibitors might be cost effective. However, the Committee was informed that there are no reliable methods of predicting which patients will gain most from these drugs.

4.3.14 Other important issues were also communicated to the Committee by the clinical experts. They reported that the Guidance issued by NICE in 2001 had brought about an improved package of care for people with dementia in the form of more expert assessments, memory clinics and regular follow-up. The Committee concluded, however, that the continuation of these facilities should not be dependent on whether these drugs are used.

Memantine

4.3.15 For moderately severe to severe AD, the Committee considered evidence from three trials of memantine (including summary results of one trial which were submitted after the Assessment Report was completed). The Committee
also took into account the economic evaluations submitted by the manufacturer and changes made to it by the Assessment Group.

4.3.16 Considering the published and unpublished evidence, the Committee concluded that the evidence for the clinical effectiveness of memantine was currently insufficient.

4.3.17 With respect to cost effectiveness, the manufacturer’s model suggested that memantine was less costly (by approximately £2000 per person) and more effective (an average QALY gain of 0.04 per person) compared with no treatment. However, the Committee had a number of concerns with the assumptions made within the evaluation and therefore with this claim of ‘dominance’. First, the RCT used to estimate the transition probabilities in the model between different severities of health showed no statistical difference (at 6 months) in MMSE scores between the memantine and control arms. Second, transition probabilities by dependency were taken from an observational study and may have been subject to bias from a number of sources. Moreover, these transition probabilities were considered to be overly optimistic given the RCT results for memantine. Third, the Committee noted that when the Assessment Group’s preferred assumptions on costs and utilities were included in the model, the resulting cost effectiveness estimates were well above those considered to be acceptable. The Committee also noted that the Assessment Group had not been able to incorporate adjustments on transition probabilities. Had these been incorporated, the estimates for cost effectiveness would have been even less favourable.
5 Proposed recommendations for further research

5.1 Research is required to find reliable means of identifying subgroups of people for whom AChE inhibitors and/or memantine are both clinically and cost-effective treatments. This concerns the refinement of measurement scales, identifying key patient characteristics that are related to benefits of AChE inhibitors treatment, and appropriate starting and stopping rules for treatment.

5.2 Longitudinal research is required to assess the relationship between carer utility (quality of life) and disease progression.

5.3 Research to generate robust and relevant data on both short- and long-term outcomes, disease progression through relevant health states, quality of life and costs of treating patients with moderately severe to severe AD with memantine is required.
6 Preliminary views on the resource impact for the NHS

6.1 This section outlines the Appraisal Committee’s preliminary assessment concerning the likely impact on NHS resources if the recommendations in Section 1 were to be implemented. When guidance is issued, this section is intended to assist NHS planners and managers in its implementation. Therefore the Institute particularly welcomes comments and information from those who would be involved in the implementation of the guidance so that this section can be made as helpful and robust as possible.


6.3 If this spending on AChE inhibitors is to be curtailed in the coming 2 years, with an expected capping at the current level for the first 6 months, it would lead to an initial release of about £15 million in funds in the year following the release of this guidance, £45 million in the second year and £60 million in the third year, all compared with present spending. There would be further savings in the form of cost avoidance in second and subsequent years, when spending in the absence of this guidance would have risen beyond £60 million.

6.4 The use of these drugs must be considered in the context of comprehensive pathways of care. There has been an expansion of specialised secondary care services, in particular the establishment and further development of memory clinics. Costs have been incurred over and above those for the drugs, memory clinics and specialist investigations, and for an increase in referrals to neurological and psychiatric services, although the scale of this is not known. As these services are worthwhile for patients with AD and are
therefore expected to continue, no significant savings are to be expected from the delivery of these specialised secondary care services.
7 Proposals for implementation and audit

This section presents proposals for implementation and audit based on the preliminary recommendations for guidance in Section 1.

7.1 NHS organisations and clinicians who care for people who have AD should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 Memantine should be prescribed only as part of ongoing or new clinical studies that are designed to generate robust and relevant data on long-term outcomes, disease progression through relevant health states, quality of life and costs.
8 Related guidance

9 Proposed date for review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 It is proposed that the guidance on this technology is considered for review in [September 2008]

Andrew Stevens
Vice-Chair, Appraisal Committee A
January, 2005
Appendix A. Appraisal Committee members and NICE project team.

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair and vice-chair between them attending meetings of all three branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett
Professor of Clinical Pharmacology, University of Leicester

Professor Sheila Bird
MRC Biostatistics Unit, Cambridge

National Institute for Clinical Excellence
Appraisal Consultation Document – Alzheimer’s disease – donepezil, rivastigmine, galantamine & memantine (review)
Issue date: February 2005
Mrs Elizabeth Brain
Patient Advocate

Dr Karl Claxton
Health Economist, University of York

Dr Richard Cookson
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Professor Christopher Eccleston
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Ms Alison Forbes
Chief Executive, Hoffman de Visme Foundation

Professor John Geddes
Professor of Epidemiological Psychiatry, Department of Psychiatry, Warneford Hospital, University of Oxford

Mr John Goulston
Director of Finance, Barts and the London NHS Trust

Dr Elizabeth Haxby
Lead Clinician in Clinical Risk Management, Royal Brompton Hospital

Dr Rowan Hillson
Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson
Clinical Lecturer in Primary Care Medicine, Alyth Health Centre, Angus, Scotland

Professor Rob Kerwin (Committee B)
Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry
Mr Muntzer Mughal
Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley

Ms Judith Paget
Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne
Health Economist, Nowgen: The North West Genetics Knowledge Park

Dr Ann Richardson
Independent Research Consultant

Professor Philip Routledge
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Debbie Stephenson
Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Chair)
Professor of Public Health, University of Birmingham

Dr Cathryn Thomas
General Practitioner, & Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter
Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr Paul Watson
Medical Director, Essex Strategic Health Authority
B. NICE  Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Meindert Boysen
Alastair Fischer
Technical Leads, NICE project team

Alec Miners
Technical Advisor, NICE project team

Alana Miller
Project Manager, NICE project team
Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessment Centre (SHTAC), University of Southampton

1. **Authors**: Emma Loveman, Colin Green, Jo Kirby, Andrea Takeda, Joanna Picot, Elizabeth Payne and Andrew Clegg

   **Title**: The Clinical and Cost-Effectiveness of Donepezil, Rivastigmine, Galantamine, and Memantine for Alzheimer’s Disease

The additional analysis was prepared by the NICE Secretariat

1. **Authors**: Meindert Boysen, Alastair Fischer and Alec Miners

   **Title**: Extra work on Appraisal of drugs for Alzheimer’s disease

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report. They are also invited to comment on the ACD and consultee organisations are provided with the opportunity to appeal against the FAD:

1. **Manufacturer/sponsors**:
   - Eisai Ltd
   - Lundbeck
   - Novartis Pharmaceuticals Ltd
   - Shire Pharmaceuticals Ltd

II Professional/specialist and patient/carer group:
III Commentator organisations (without the right of appeal):

- British National Formulary
- National Collaborating Centre for Chronic Conditions
- National Public Health Service for Wales
- NHS Quality Improvement Scotland
- Institute for Ageing and Health
- Alzheimer’s Research Trust
- Dementia Research Group and Department of Old Age Psychiatry, Institute of Psychiatry
- Research Institute for the Care of the Elderly

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee’s deliberations. They gave their expert personal view on Alzheimer’s disease – donepezil, rivastigmine, galantamine & memantine (review) by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD:

- Mrs Louise Chambers, Chief Executive, Dementia Care Trust
- Mrs Carol O'Connor, Pharmaceutical Consultant
- Professor John T O'Brien, Professor, Old Age Psychiatry, Institute for the Ageing and Health
- Mr Mervyn Richardson, Retired Consultant for the United Nations
- Mr Gordon Wilcock, Professor, Care of the Elderly, University of Bristol
- Dr David Wilkinson, Consultant in Old Age Psychiatry, Chair Older People’s Mental Health Directorate, Hampshire Partnership NHS Trust
- Prof Roy Jones, Director, The Research Institute for the Care of the Elderly