

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

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

This guidance constitutes a review of *NICE technology appraisal* no.19 on the use of donepezil, galantamine and rivastigmine for the treatment of mild to moderate Alzheimer's disease, published in 2001, and a new appraisal of the clinical and cost effectiveness of memantine.

1 Guidance

This guidance relates to the approved licensed indications for the treatments under consideration – that is, mild to moderately severe Alzheimer's disease for donepezil, galantamine and rivastigmine, and moderate to severe Alzheimer's disease for memantine.

The benefits of these drugs for patients with other forms of dementia (for example, vascular dementia or dementia with Lewy bodies) have not been assessed in this guidance.

- 1.1 The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of people with Alzheimer's disease of moderate severity only (that is, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions.

- Only specialists in the care of people with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate

treatment. Carers' views on the patient's condition at baseline should be sought.

- Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.

- 1.2 When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions, and dosing profiles.
- 1.3 Memantine is not recommended as a treatment option for people with Alzheimer's disease except as part of well designed clinical studies.
- 1.4 People with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and people with Alzheimer's disease currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist consider it 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. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features.
- 2.2 Alzheimer's disease is usually insidious in onset and develops slowly but steadily over a period of several years. It affects predominantly the elderly. Progression is characterised by deterioration in cognition (thinking, conceiving, reasoning) and functional ability (activities of daily living) and a disturbance in behaviour and mood. Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition. Evidence suggests that Alzheimer's disease progression is dependent on age, and the time from diagnosis to death is about 5–20 years (median 5 years in people aged 75–80 years).
- 2.3 People with Alzheimer's disease lose the ability to carry out routine daily activities like dressing, 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 affected by the burden of providing care. 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.
- 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 Alzheimer's Disease

Assessment Scale – cognitive subscale (ADAS-cog – 70 points) or the Mini Mental State Examination (MMSE – 30 points) for cognitive outcomes. MMSE score, for example, denotes the severity of cognitive impairment as follows:

- mild Alzheimer's disease: MMSE 21 to 26
- moderate Alzheimer's disease: MMSE 10 to 20
- moderately severe Alzheimer's disease: MMSE 10 to 14
- severe Alzheimer's disease: MMSE less than 10.

2.6 Population data (2002) for England and Wales show an estimated prevalence of 290,000 people with Alzheimer's disease. 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 Alzheimer's disease. The incidence rate for Alzheimer's disease in people over the age of 65 years 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 a higher risk than men). In people with Alzheimer's disease, 50–64% are estimated to have mild to moderately severe disease, and approximately 50% have moderately severe to severe Alzheimer's disease.

2.7 People with mild dementia are sometimes able to cope without assistance, but as the disease progresses, all eventually require the aid of carers, and about half need residential care. The total cost of care for people with dementia is estimated by the Audit Commission to be £6 billion per year in England, 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 in a number of circumstances for those with suspected dementia, 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, galantamine, rivastigmine

- 3.1 Acetylcholinesterase (AChE) inhibitors increase the concentration of acetylcholine at sites of neurotransmission. Since the original NICE guidance of 2001 the number of prescribed defined daily doses for AChE inhibitors, especially donepezil, has increased markedly. Substantial regional variation in the number of prescriptions is seen across Strategic Health Authorities in England and Wales.
- 3.2 Donepezil (Aricept, Eisai Ltd) is a specific and reversible inhibitor of AChE, licensed in the UK at a dosage of 5 mg/day and 10 mg/day. It is licensed for the symptomatic treatment of people with 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]* 50th edition, September 2005). This equates to £828.29 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 Galantamine (Reminyl, Shire Pharmaceuticals Ltd) is a selective, competitive and reversible inhibitor of AChE, licensed in the UK. It is licensed for the symptomatic treatment of people with mild to moderately severe dementia of the Alzheimer type. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor. The maintenance dosage is 8–12 mg twice daily. Prices are £68.32 for 56 tablets and modified release capsules of 8 mg and £84.00 for 56 tablets and modified release capsules of 12 mg (excluding VAT; *BNF* 50th edition, September 2005). This equates to £890.60 and £1095.00 per

year of treatment, respectively. Costs may vary in different settings because of negotiated procurement discounts.

- 3.4 Rivastigmine (Exelon, Novartis Pharmaceuticals UK Ltd) is an acetylcholinesterase and butyrylcholinesterase inhibitor, licensed in the UK. It is licensed for symptomatic treatment of people with mild to moderately severe Alzheimer's dementia. The usual maintenance dosage is 3–6 mg twice daily. Prices are £68.04 for 56 capsules of 1.5 mg, 3 mg, 4.5 mg and 6 mg (excluding VAT; *BNF* 50th edition, September 2005). This equates to £886.95 per year of treatment. Costs may vary in different settings because of negotiated procurement discounts.
- 3.5 Typical side effects of donepezil, galantamine and rivastigmine are related to the gastrointestinal tract (including nausea and vomiting). These side effects are dose related and although they are usually short term they can lead to non-adherence. For full details of side effects and contraindications, see the Summaries of Product Characteristics.

Memantine

- 3.6 Memantine (Ebixa, Lundbeck Ltd) is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA)-receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. It is used in the treatment of people with moderate to severe Alzheimer's disease. The recommended maintenance dosage is 10 mg twice daily. Prices are £69.01 for 56 tablets of 10 mg (excluding VAT; *BNF* 50th edition, September 2005). This equates to £899.59 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 dizziness, headache, constipation and somnolence. For full details of side effects and contraindications, see the Summary of Product Characteristics.

4 Evidence and interpretation

The Committee (Appendix A) reviewed the data available on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, having considered evidence on the nature of the condition and the value placed on the benefits of donepezil, galantamine, rivastigmine and memantine by people with Alzheimer's disease, those who represent them, and clinical experts (Appendix B). It was also mindful of the need to take account of the effective use of NHS resources.

4.1 *Clinical effectiveness*

Mild to moderately severe Alzheimer's disease

- 4.1.1 The quality of the reporting and methods of the included published randomised controlled trials (RCTs) of the AChE inhibitors (donepezil, galantamine and rivastigmine) was mixed.

4.1.2 Donepezil

- 4.1.2.1 Thirteen published 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 up participants for longer than 6 months.

- 4.1.2.2 Six RCTs reviewed by the Assessment Group showed a statistically significant improvement in cognition following treatment with donepezil

compared with placebo, as assessed using the ADAS-cog scale. Higher doses of donepezil were associated with increasing benefit. Three RCTs with a duration of 12–24 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 on the ADAS-cog was found for the 5 mg daily dose (aggregate number of people randomised 850) 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 (aggregate number of people randomised 608). 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 following treatment with donepezil compared with placebo. Results of a meta-analysis performed by the Assessment Group on two of these RCTs (aggregate number of people randomised 610) showed a change from baseline in MMSE score of 1.30 (95% CI 0.78 to 1.82) for 10 mg donepezil when compared with placebo. One UK study (486 people randomised), excluded from the meta-analysis by the Assessment Group, used MMSE as a secondary outcome and showed that, over the first 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 , $p < 0.0001$).
- 4.1.2.4 Seven RCTs (aggregate number of people randomised 2460) assessed the effect of donepezil compared with placebo on global outcomes, using the CGIC or CIBIC-plus. There was a statistically significant greater change from baseline (improvement) in CGIC or CIBIC-plus scores following treatment with donepezil compared with placebo.
- 4.1.2.5 Studies reporting on the effects of donepezil on functional outcomes in people with Alzheimer's disease (using a variety of measures of activities

of daily living) generally found better, or less deterioration in, functional ability than for placebo, although these findings were not statistically significant in any of the trials. These trials generally measured changes in functional outcomes over treatment periods of 24 or 52 weeks. One UK study (486 people randomised) that measured rates of institutionalisation as a primary outcome for as long as 3 years found some differences between donepezil and placebo at 1 year (9% donepezil versus 14% placebo), although this difference was not statistically significant ($p = 0.15$) and not sustained at 3 years (42% donepezil versus 44% placebo, respectively, $p = 0.4$). Results for the other primary outcome – progression of disability – showed little difference at 1 year and no benefit at 3 years (13% donepezil versus 19% placebo at 1 year; 55% versus 53%, respectively, at 3 years); again these differences were not statistically significant.

- 4.1.2.6 Quality-of-life estimates for people with Alzheimer's disease 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 on this set of health measurements is unclear. One study showed improvement in quality of life, another showed no change and the third showed worsening of quality of life. The effect of the dose of donepezil used was unclear in all three studies.
- 4.1.2.7 Behavioural symptoms were measured using the neuropsychiatric inventory (NPI) in four RCTs of donepezil. The results varied but generally a small and statistically significant effect was found for donepezil compared with placebo on improving or limiting further deterioration on the NPI scale in the short term.
- 4.1.2.8 Adverse events were recorded more frequently in participants treated with donepezil compared with those receiving placebo, and numbers of adverse events increased with higher doses of donepezil. Similar numbers of participants in the low-dose donepezil groups and the placebo groups

withdrew from the studies because of adverse events. However, higher numbers of participants in the higher dose group withdrew because of adverse events.

- 4.1.2.9 The manufacturer's submission included a 24-week RCT that evaluated the safety and efficacy of donepezil treatment compared with placebo in people with moderately severe Alzheimer's disease (baseline MMSE score 5–17). 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 in the 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 carer).
- 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 (5 or 10 mg/day) for 153 people who had not shown a response ('no apparent clinical benefit') after 24 weeks of open-label donepezil treatment. Double-blind treatment was continued for 12 weeks and there was a statistically significantly greater mean improvement in MMSE score (1.62 versus 0.49) and NPI scale (–2.40 versus 0.76) following treatment with donepezil (10 mg/day) versus placebo, respectively.
- 4.1.2.11 In further analyses using the manufacturer's intention to treat – last observation carried forward (ITT-LOCF) data from five RCTs of at least 24 weeks (aggregate number of people randomised 1425) and applying the responder definition presented in *NICE technology appraisal guidance no.19 (TA no. 19)*, the MRC Biostatistics Unit reported in their review that 39% (95% CI 23% to 56%) of people on donepezil would have been a responder compared with 22% (95% CI 11% to 34%) on placebo. The magnitude of response of these responders on donepezil, expressed as

the change from baseline on ADAS-cog versus the change from baseline on ADAS-cog of all on placebo, was -6.26 (95% CI -7.80 to -4.72). The corresponding group of responders on placebo showed a magnitude of response of -5.27 (95% CI -6.90 to -3.64), while the non-responders on donepezil showed a magnitude of response of -1.21 (95% CI -2.11 to -0.30) and on placebo 0.99 (95% CI 0.04 to 1.94). When using an alternative definition of response (no change or improvement on ADAS-cog) the manufacturer reported a response rate of 63% for those people on donepezil and 41% for those on placebo. The magnitude of change from baseline compared with all placebo reported by the manufacturer was -5.82 .

4.1.2.12 Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITT-LOCF data from the trials of at least 24 weeks, reported for donepezil a magnitude of change from baseline on ADAS-cog of -2.03 (99% CI -3.36 to -0.71) for people with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 546), of -3.94 (99% CI -7.05 to -0.83) for people with moderate Alzheimer's disease (MMSE 15 to 20; aggregate number of people randomised 396) and of -3.63 (99% CI -7.98 to 0.72) for people with moderately severe Alzheimer's disease (MMSE 10 to 14; aggregate number of people randomised 253) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. When ADAS-cog was used for the definition of severity, the magnitude of change from baseline reported for people with mild cognitive impairment (ADAS-cog 4–28) was -3.24 (99% CI -7.10 to 0.62) and -3.91 (99% CI -8.64 to 0.64) for people with moderate cognitive impairment (ADAS-cog 29–61). Comparable proportions of people were mild, moderate and moderately severe at baseline in the donepezil and placebo groups.

4.1.2.13 Responder analyses for each of the three subgroups stratified according to cognitive impairment (based on MMSE) and using the responder definition of TA no. 19 resulted in 34% of the people using donepezil in the mild

cohort, 31% in the moderate cohort and 10% in the moderately severe cohort retrospectively being designated a responder. The magnitude of response (analysis of observed cases) reported for these three subgroups was -5.12 (95% CI -6.82 to -3.43), -10.14 (95% CI -13.55 to -6.73) and -6.32 (95% CI -13.11 to 0.47) for mild, moderate and moderately severe, respectively.

4.1.2.14 In summary, evidence from studies using cognitive and global outcome measurement scales suggests that donepezil is beneficial in treating Alzheimer's disease. The effect of donepezil on quality of life and behavioural symptoms in Alzheimer's disease is less clear. Short-term benefits are seen on scales that measure functional outcomes but these were not always statistically significant and do not seem to be sustained in the long term. Retrospective responder analyses using the TA no. 19 and subgroup analyses based on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

4.1.3 Galantamine

4.1.3.1 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. (TA no. 19 was based on one systematic review, three RCTs and three unpublished studies from the manufacturer.) All comparisons were versus placebo, with trials reporting dosages of 8–36 mg/day and durations of 3–6 months.

4.1.3.2 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 conferred a statistically significant benefit to participants when compared with placebo. The benefit varied depending

on the dose of galantamine. Four RCTs that assessed treatment with galantamine at a dose of 24 mg were combined by the Assessment Group in a meta-analysis. The fixed-effects model showed a weighted mean difference of -3.28 (95% CI -3.89 to -2.67), representing a statistically significant improvement following treatment with galantamine versus placebo.

- 4.1.3.3 Six RCTs assessed the effect of galantamine compared with placebo on the CIBIC-plus scale. They showed that, in individual studies, more participants on galantamine improved than on placebo (0–6.5 percentage points more), whereas more participants on placebo than on galantamine deteriorated (4–18 percentage points 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.
- 4.1.3.4 The results of two RCTs showed that participants receiving galantamine at dosages of 16–32 mg/day had statistically significantly less deterioration than those receiving placebo, as assessed using scales that measure activities of daily living.
- 4.1.3.5 In one RCT, higher dosages of galantamine (16 mg/day or over) were associated with a statistically significant slowing in the deterioration of participants' behavioural condition compared with placebo, as assessed using the NPI scale. In two trials, the slowing of deterioration was not statistically significantly different between galantamine and placebo groups.
- 4.1.3.6 Across RCTs, between 2 and 27 percentage points more participants on galantamine experienced an adverse event compared with those on placebo. Between 6% and 44% of participants receiving galantamine withdrew from the studies because of adverse events, and this number increased with higher doses of galantamine.

- 4.1.3.7 The manufacturer's submission presented a pooled analysis of two 6-month RCTs in people with mild to moderate Alzheimer's disease. The results showed a statistically significant decrease in the overall mean amount of time that carers spent assisting people with activities of daily living. The decrease was 32 minutes/day for participants 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.
- 4.1.3.8 In 6-week follow-on studies of two RCTs (aggregate number of people randomised 570), included in the manufacturer's submission, people who were switched from galantamine to placebo experienced a greater decline in measures of cognition than those who remained on galantamine. This difference reached statistical significance only in the study where the decision to stop treatment was not randomised (number of participants 500).
- 4.1.3.9 In further analyses using the manufacturer's ITT-LOCF data from five RCTs of at least 24 weeks (aggregate number of people randomised 2682) and applying the responder definition presented in TA no. 19, the MRC Biostatistics Unit reported that 41% (95% CI 31% to 51%) of people on galantamine would have been a responder compared with 27% (95% CI 20% to 35%) on placebo. The magnitude of response of these responders on galantamine, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAS-cog of all on placebo, was -6.40 (95% CI -7.15 to -5.65). The corresponding group of responders on placebo showed a magnitude of response of -5.28 (95% CI -5.93 to -4.63), while the non-responders on galantamine showed a magnitude of response of -0.44 (95% CI -1.83 to 0.94) and on placebo, 2.05 (95% CI 1.35 to 2.74). When using alternative definitions of response (no change or improvement on ADAS-cog and on global measures; no change, no improvement, or deterioration no more than 4 points on the

ADAS-cog) a response rate of 57% and 87%, respectively, for those people on galantamine and 20% and 17%, respectively, for those on placebo was reported. The magnitude of change from baseline compared with all those on placebo by the manufacturer was -6.26 (95% CI -6.87 to -5.66) and -4.33 (95% CI -4.89 to -3.77) for the first and second alternative definitions of responders, respectively.

- 4.1.3.10 Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITT-LOCF data from the trials of at least 24 weeks, reported for galantamine a magnitude of change from baseline on ADAS-cog of -2.40 (99% CI -3.33 to -1.47) for people with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 938), of -4.1 (99% CI -5.03 to -3.17) for people with moderate Alzheimer's disease (MMSE 10 to 20; aggregate number of people randomised 1215; includes the moderately severe) and of -6.1 (99% CI -7.93 to -4.27) for people with moderately severe Alzheimer's disease (MMSE 10 to 14; aggregate number of people randomised 340) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. Comparable proportions of people were mild, moderate and moderately severe at baseline in the galantamine and placebo groups.
- 4.1.3.11 In summary, evidence from studies using cognitive and functional outcome measurement scales suggests that galantamine is beneficial in Alzheimer's disease. 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 that higher proportions of participants improved with galantamine, but this was not reflected in the meta-analysis. In some studies, considerably more participants withdrew because of adverse events. Retrospective responder analyses using the TA no. 19 and subgroup analyses on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the

Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

4.1.4 Rivastigmine

- 4.1.4.1 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. (TA no. 19 was based on three systematic reviews, five RCTs and two unpublished studies from the manufacturer.) All published comparisons were versus placebo, and trials reported dosages of between 1 mg/day and 12 mg/day with durations of 26 weeks or less.
- 4.1.4.2 Four RCTs reviewed by the Assessment Group showed that rivastigmine within its licensed maintenance dose (6–12 mg/day, mean dosage approximately 10 mg/day) conferred a statistically significant benefit to participants when compared with placebo, as measured using the ADAS-cog scale. One RCT found no significant differences. No statistically significant effects were seen in the low-dose treatment groups in these studies. A meta-analysis, using a fixed-effects model, of two RCTs both with a duration of 26 weeks, was associated with a weighted mean difference of -3.08 (95% CI -3.78 to -2.38) for rivastigmine 6–12 mg/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 in the fixed-effects model should be treated with caution.
- 4.1.4.3 Four RCTs showed statistically significantly higher MMSE scores in the groups treated with rivastigmine within its licensed maintenance dose regime (6–12 mg/day) compared with placebo.

- 4.1.4.4 Four RCTs assessed the effect of rivastigmine compared with placebo on the CIBIC-plus scale. In the two published RCTs, statistically significant mean improvements were recorded following treatment with rivastigmine in the high-dose – licensed - regimen only, compared with placebo. The percentage of improvers or responders on the CIBIC-plus scale was also calculated in these two published studies. Clinical improvement was defined as a score of 1, 2 or 3 on the CIBIC-plus scale. For the two trials, 16–20% of participants treated with placebo were judged to have responded versus 30–57% of those treated with rivastigmine. A statistically significant difference was found for the high-dose regimen only.
- 4.1.4.5 Generally, participants treated with rivastigmine 6–12 mg/day demonstrated statistically significantly better functional outcomes than those who received placebo. One of the four studies using the PDS showed that there was no statistically significant difference for either the low- or high-dose regimen when compared with placebo.
- 4.1.4.6 The Nurses Observation Scale for Geriatric Participants (NOSGER) was used in two rivastigmine RCTs. Statistically significant benefits were seen on the subscale that measures impact on memory but no statistically significant benefits were demonstrated on measures of mood and behaviour in the groups treated with rivastigmine compared with the placebo groups.
- 4.1.4.7 The percentage of participants reporting adverse events, namely nausea and vomiting, resulting from treatment with rivastigmine was particularly high in those treated at a higher dose. The number of participants who withdrew because of adverse events was reported in all studies. Estimates of the percentage of participants who withdrew varied considerably between studies; 7–28.6% for participants receiving treatment and 4–7.2% for participants receiving placebo.

- 4.1.4.8 The manufacturer's submission included a number of open-label and observational studies. 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 that 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 carer burden.
- 4.1.4.9 The manufacturer's submission included a prospective, open-label study that evaluated the efficacy, safety and 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% of the 382 participants had responded to rivastigmine (defined as improvement or stabilisation of symptoms using the CGIC).
- 4.1.4.10 In further analyses using the manufacturer's ITT-LOCF data from four RCTs of at least 24 weeks (aggregate number of people randomised 1670) and applying the responder definition presented in TA no. 19, the MRC Biostatistics Unit reported that 37% (95% CI 30% to 44%) of people on rivastigmine would have been a responder compared with 24% (95% CI 18% to 30%) on placebo. The magnitude of response of these responders on rivastigmine, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAS-cog of all on placebo, was -6.83 (95% CI -8.25 to -5.40). The corresponding group of responders on placebo showed a magnitude of response of -5.57 (95% CI -6.49 to -4.65), while the non-responders on rivastigmine showed a magnitude of response of -0.40 (95% CI -1.94 to 1.13) and on placebo, 1.81 (95% CI 1.07 to 2.55).
- 4.1.4.11 Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITT-LOCF data from the trials of at least 24 weeks, reported for rivastigmine a magnitude of change from baseline on ADAS-cog of -1.20 (99% CI -2.10 to -0.30) for people

with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 734), of -3.7 (99% CI -5.13 to -2.27) for people with moderate Alzheimer's disease (MMSE 10 to 20; aggregate number of people randomised 557) and of -5 (99% CI -7.40 to -2.6) for people with moderately severe Alzheimer's disease (MMSE 10 to 14; aggregate number of people randomised 232) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. When ADAS-cog was used for the definition of severity, the magnitude of change from baseline reported for people within a number of strata for cognitive impairment was -0.4 (99% CI -1.37 to 0.57) (ADAS-cog 0–12), -1.7 (99% CI -2.85 to -0.55) (ADAS-cog 13–20), -2.6 (99% CI -4.22 to -0.95) (ADAS-cog 21–28), -4.9 (99% CI -7.28 to -2.52) (ADAS-cog 29–36), -5.9 (99% CI -8.86 to -2.94) (ADAS-cog 37–44) and -3.9 (99% CI -7.38 to -0.42) (ADAS-cog 45 plus). Comparable proportions of people were mild, moderate and moderately severe at baseline in the rivastigmine and placebo groups.

- 4.1.4.12 In summary, a range of fixed and flexible dosing regimens of rivastigmine was investigated across studies, which makes interpretation of the evidence more difficult. Evidence from studies using cognitive and global outcome measurement scales suggests that rivastigmine is beneficial in Alzheimer's disease at higher doses (6–12 mg). Evidence for an effect on functional outcomes was less conclusive and no statistically significant benefit of rivastigmine on measures of behaviour and mood was reported. Higher doses of rivastigmine were associated with considerable adverse effects and these effects caused withdrawals from studies. The results of the meta-analysis on cognition should be treated with caution because of statistically significant heterogeneity between individual trial results. Retrospective responder analyses using the TA no. 19 and subgroup analyses on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute

and suggest some differential advantage for more severely cognitively impaired subgroups.

4.1.5 Head-to-head comparisons

- 4.1.5.1 Three RCTs met the inclusion criteria for the systematic review by the Assessment Group. Two compared donepezil with rivastigmine (aggregate number of people randomised 139) and one compared donepezil with galantamine (people randomised 120). 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 population was not described as patients with mild to moderately severe Alzheimer's disease by any definition and the MMSE scores fell outside the range of 10–26.
- 4.1.5.2 For the two RCTs that compared donepezil with rivastigmine, the difference in change from baseline, in measures of cognition or function, was small and not statistically significant. The number 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 instead of the scheduled dose titration that was used in one of these trials.
- 4.1.5.3 In the RCT that compared galantamine and donepezil, which 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.

Moderately severe to severe Alzheimer's disease

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. (TA no. 19 did not consider memantine.) Both studies reported on participants with moderately severe to severe Alzheimer's disease, as measured by the MMSE, and treated with memantine 20 mg/day. One study compared memantine alone with placebo over a period of 28 weeks, and the other compared memantine plus donepezil with donepezil alone over 24 weeks. In the second study, participants were included on the basis that they had already been receiving donepezil for more than 6 months before entering the trial, and they had been at a stable dosage (5–10 mg/day) for at least 3 months. These participants were maintained on stable donepezil for the duration of the study. Additionally, people were only included in this trial if they had received a diagnosis of Alzheimer's disease within the last 12 months. The quality of reporting and methods of the two trials was generally good.
- 4.1.6.2 In the RCT of memantine versus placebo, less deterioration of cognitive function was recorded following treatment with memantine compared with placebo, as measured by the Severe Impairment Battery (SIB) (mean change from baseline at end point LOCF analysis for memantine and placebo was –4.0 and –10.1, respectively, $p < 0.001$), the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) (mean changes from baseline at end point LOCF analysis: –3.1 and –5.2, $p = 0.02$) and the Functional Assessment Staging scale (FAST) (mean changes from baseline at end point LOCF analysis: –0.2 and 0.6, $p = 0.02$). No statistically significant differences were recorded using CIBIC, MMSE and NPI when changes from baseline to end point were analysed using LOCF.
- 4.1.6.3 In the RCT in which participants received memantine and donepezil in combination, less deterioration in cognitive function was recorded in

participants receiving combined treatment compared with donepezil alone, as measured by the SIB (mean change from baseline at end point LOCF for memantine plus donepezil and donepezil alone was 0.9 and 2.5, respectively, $p < 0.001$), ADCS-ADL (mean changes from baseline at end point LOCF: -2.0 and -3.4 , $p = 0.03$), NPI (mean changes from baseline at end point LOCF: -0.1 and 3.7 , $p = 0.002$) and CIBIC-plus (mean changes from baseline at end point LOCF: -4.41 and -4.66 , $p = 0.03$).

- 4.1.6.4 During the course of this review and after the Assessment Report had been produced, a further trial, in people with moderately severe to severe Alzheimer's disease (memantine versus placebo), was identified. The manufacturer of memantine then provided summary results commercially-in-confidence after which summary data were to be published on the website of the American sponsor of memantine. The results expressed as changes from baseline at end point LOCF were less favourable towards memantine than those of the published RCT of memantine versus placebo; mean change from baseline at endpoint (LOCF) on SIB reported for memantine -2.0 and for placebo -2.5 , $p = 0.616$; on ADCS-ADL -2.0 and -2.7 , $p = 0.282$; on CIBIC-Plus 4.3 and 4.6 , $p = 0.182$ and on NPI 1.0 and 1.1 , $p = 0.963$; respectively for memantine and placebo.
- 4.1.6.5 The manufacturer of memantine also provided summary results from a number of pooled analyses. In one analysis, data for all three RCTs showed less deterioration in cognitive function for patients receiving memantine as measured by the SIB (mean change from baseline for memantine [\pm donepezil] versus placebo [\pm donepezil] was -1.97 and -5.14 , respectively, $p < 0.001$), ADCS-ADL (mean changes from baseline: -2.92 and -4.18 , $p = 0.002$), NPI (mean changes from baseline: 0.05 and -1.00 , $p = 0.02$) and CIBIC-plus (mean changes from baseline: 4.46 and 4.7 , $p < 0.001$). When the analysis was restricted to patients in only the two memantine monotherapy RCTs, the results were less favourable towards memantine than in the pooled analysis of all three RCTs.

4.1.6.6 Similar pooled analyses were undertaken for patients who were subclassified as 'behaviourally disturbed', defined as a score > 0 on any of the NPI sub-item scores for three specific items: agitation/aggression; delusions and hallucinations. Patients had to score > 0 on any of the three items at baseline to qualify. For the analyses containing all three RCTs, less deterioration in cognitive function for patients receiving memantine as measured by the SIB (mean change from baseline for memantine [\pm donepezil] versus placebo [\pm donepezil] was -1.59 and -6.69 , respectively, $p < 0.001$), ADCS-ADL (mean changes from baseline at end point LOCF: -2.87 and -4.76 , $p = 0.001$), NPI-cluster of the three sub-items used for the definition of the subgroup (mean changes from baseline at end point LOCF: -0.65 and 0.74 , $p < 0.001$) and CIBIC-plus (mean changes from baseline at end point LOCF: 4.54 and 4.88 , $p < 0.001$) was observed. When the analysis was restricted to patients in only the two memantine monotherapy RCTs, the results were less favourable towards memantine in terms of the differences in change from baseline at endpoint LOCF compared with placebo than in the pooled analysis of all three RCTs.

4.1.6.7 Memantine's manufacturer also supplied a 'responder analysis', which itself was restricted to further consideration of only the 'behaviourally disturbed' subgroup, where a responder was defined as an improvement or no worsening of CIBIC-plus scores at 6 months using data from one of the monotherapy RCTs. Differences in the proportions of patients responding while using memantine compared with those using placebo ranged from 10.4% ($p = 0.044$) to 18.7% ($p < 0.001$) depending on the choice of RCT(s) and the outcome measure of interest (that is, SIB, ADCS-ADL, CIBIC-plus or NPI-cluster). Versus all those on placebo the differences in proportions of patients responding on memantine ranged between 17.4% and 27.8%.

4.1.6.8 A fourth RCT was also referenced by the manufacturer of memantine. This compared memantine with placebo, and a proportion ($n = 79$, 48%) of

participants had moderately severe to severe Alzheimer's disease.

Although different outcome instruments were used in this trial, the results were broadly in line with findings from the other three RCTs.

- 4.1.6.9 The frequency of overall adverse effects was similar for both the memantine and control groups in all RCTs.

4.2 **Cost effectiveness**

- 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 its preferred assumptions, and it also presented an additional economic evaluation of the three AChE inhibitors. Further analyses were undertaken by the NICE secretariat as described in technical report number 1 and the addendum.

Mild to moderately severe Alzheimer's disease

4.2.2 Donepezil

- 4.2.2.1 Eleven economic evaluations for donepezil were found. Three related to the UK. One of the 11 studies was of treatment for people with mild Alzheimer's disease; the other ten were of treatment of people with mild to moderate Alzheimer's disease. 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 (QALY) gained (CQG) for 5 mg/day of £21,000 (2-year model) to £86,000 (10-year model) for an average 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 estimated cost

ranged from £1200 to £7000, depending on dose and starting point (mild or moderate Alzheimer's disease).

- 4.2.2.4 In a recent economic analysis alongside a clinical trial, the authors concluded that the drug was not cost effective, mainly because there were no apparent benefits of the drug in delaying progression of disability or entry to institutional – that is, residential – nursing or NHS continuing care.
- 4.2.2.5 The manufacturer's model used a transition state modelling approach in which disease progression was modelled across different levels of Alzheimer's disease 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 Alzheimer's disease by MMSE score. The submission reported that, for the base case of people with an MMSE score of 13–26, treatment with donepezil 10 mg/day was associated with an estimated cost of £1200 to keep a person outside of the severe Alzheimer's disease state for a year. Inclusion of people with an MMSE score 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 utility estimates or 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 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 Alzheimer's disease, this incremental cost effectiveness translated to an estimated CQG of £45,000.

4.2.3 Galantamine

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

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

4.2.3.3 The manufacturer's submission also included a cost-effectiveness analysis for galantamine using the AHEAD modelling framework. The AHEAD model rests on the concept of need for full-time care, and it simulates the experience of a cohort of people with Alzheimer's disease across three possible health states: pre-full-time care, full-time care 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 time to estimate the likelihood of disease progression over time to a level at which full-time care is required. Parameters used in the predictive risk/hazard equations for full-time care 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). While the prevalence of 'psychotic symptoms' used to establish the original risk equation was based on the Columbia University Scale for psychopathology in Alzheimer's disease, the submitted model instead used two different measures for its approximation of prevalence

and effect of the drug (for example, prescription of antipsychotic medication during the trial and hallucinations or delusions subscales of the NPI). Baseline characteristics of the patients from three clinical trials were used to inform these parameters but a variety of scales for each of them were combined and exact details were not presented. Cost estimates in the model were taken from published UK data. Health-state utility data were taken from a cross-sectional study of carers of Alzheimer's disease 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 full-time care of 3.0 months, which equates to 0.07 QALYs and a CQG of £10,000. The model predicted net savings for people with moderate Alzheimer's disease (MMSE < 18) and for those who showed response to treatment after 6 months. However, no details were given on how responders could be distinguished from other patients and to what extent they benefited more than non-responders on the parameters used in the risk equation for full-time care.

- 4.2.3.4 Although the Assessment Group noted that the structure of the model involved only two health states and that this may be seen as a crude reflection of the natural history of Alzheimer's disease, they accepted that these states are relevant. The Assessment Group expressed concerns that the risk equations had been derived from an observational study in the USA, that there was a need to transform the ADAS-cog or MMSE scores to reflect an mMMS score and that the model predicts death rates that may be an underestimate of the mortality expected in the UK treatment-eligible patient group. Nevertheless, the Assessment Group indicated that the AHEAD model structure could be seen to be the best available way to illustrate potential progression of Alzheimer's disease 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.

4.2.4 Rivastigmine

- 4.2.4.1 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 Alzheimer's disease. Four, including all three industry-associated studies, were found to be cost saving.
- 4.2.4.2 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 were associated with 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.
- 4.2.4.3 In a study supported by the manufacturer, for people using the drug compared with not using it, estimated cost savings (but not including the cost of rivastigmine) after 2 years were £1300 for people with mild Alzheimer's disease and £800 for those with moderate Alzheimer's disease.
- 4.2.4.4 The manufacturer's submission detailed a 5-year model that combined data on clinical pathways from a trial, a statistical model of the natural history of Alzheimer's disease using MMSE and a mapping process estimating utility values for Alzheimer's disease 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.
- 4.2.4.5 The Assessment Group expressed specific concerns about the method used to derive a QALY value in the manufacturer's model, especially where it was related to the MMSE. Apart from incorporating alternative cost estimates in the manufacturer's model, the Assessment Group also

halved the proposed utility benefit resulting from a one-unit change in MMSE score. These adjustments led to a CQG estimate of £46,000.

4.2.5 Assessment Group model

- 4.2.5.1 The Assessment Group extended the framework of the AHEAD model in order to develop a model of disease progression that allowed for all three AChE inhibitors to be modelled using the same framework. The model estimated 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 Alzheimer's disease were modelled in a Markov disease progression model over a time horizon of 5 years. The predictive risk equation for full-time care of the AHEAD model was used unchanged, while an annual mortality rate of 11.2% replaced the risk equation for mortality used in AHEAD.
- 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-full-time care and full-time care health states were estimated after the Group reviewed the literature, and results from numerous sources were combined. The Assessment Group assumed that only 70% of costs of full-time care in an institutional setting would be met by the NHS. The Assessment Group used the health-state utility data from the US cross-sectional study of carers of people with Alzheimer's disease. A utility value of 0.60 for the pre-full-time care and of 0.34 for the full-time care health state were assumed to be appropriate estimates considering those utilities reported in the literature and the AHEAD model, combined with a comparison with the EuroQoL EQ-5D tariff method. By assigning these utilities to the two health states the AHEAD model resulted in a loss of 0.26 utility whenever a patient in the model were to transit between the two 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 at

baseline, Alzheimer's disease duration, effectiveness of the intervention expressed as an incremental change in ADAS-cog score, monitoring costs, costs for pre-full-time care and full-time care, and health utilities).

- 4.2.5.3 The results of the Assessment Group model were presented both deterministically and probabilistically. The probabilistic analysis of the model was associated with a difference in time spent in full-time care over 5 years ranging from 1.41 to 1.54 months, and QALYs gained ranged from 0.032 to 0.035, depending on the AChE inhibitor used. The resulting base-case CQGs were £97,000 for donepezil (10 mg daily), £82,000 for galantamine (24 mg daily) and £70,000 for rivastigmine (6–12 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.

4.2.6 Extra analyses undertaken by NICE's secretariat

- 4.2.6.1 At the request of the Appraisal Committee, 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 behavioural 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 people who, at the end of the time horizon of the Assessment Group's model, would not have had the capacity to benefit – that is, people who died in pre-full-time care or who were in pre-full-time care 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-full-time care health state should be 0.69 instead of 0.60, resulting in a difference of 0.35 between pre-full-time care and full-time care health states. A separate analysis was also undertaken that estimated the impact of including carer benefits.

- 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 section 4.2.6.1, as well as the increase in utility for pre-full-time care. 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. Estimates of CQG presented here for the augmented base case use the assumption that 70% of costs of institutional care are being met by the NHS/PSS (Personal Social Service). The complete augmented base case was associated with an estimated CQG of £54,000, £46,000 and £39,000 for donepezil, galantamine and rivastigmine, respectively (including a correction for the coefficient 'age at onset' used in the risk-equation for 'full-time care', a price adjustment for donepezil and an adjustment in the results of the meta-analysis of effectiveness for galantamine). This equates to a respective average QALY gain of 0.058, 0.062 and 0.060.
- 4.2.6.3 There is very little quantitative evidence related to carer utilities and the evidence that exists suggests that utility scores for the carers were insensitive to people's Alzheimer's disease stage and setting. When an assumed 0.01 of carer utility was included in a sensitivity analysis on the augmented base case, either as a direct benefit or as part of the total increment between the two health states of the Assessment Group's model, this was associated with marginally lower estimates of the CQG: £50,000, £44,000 and £36,000 for donepezil, galantamine and rivastigmine, respectively.

- 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 neuropsychiatric or behavioural symptoms was used to assess the impact on the CQG estimates. On its own, changing the estimates of effects of therapy on neuropsychiatric or behavioural symptoms made no substantial difference to the CQG for the augmented base case. However, when the intermediate estimate of prevalence of neuropsychiatric or behavioural symptoms (30%) was combined with an assumed effect of treatment (20% reduction) the resulting estimated CQG was £47,000, £39,000 and £35,000 for donepezil, galantamine and rivastigmine, respectively. When this one-way sensitivity analysis on neuropsychiatric or behavioural symptoms was combined with the assumptions on carer benefits (see 4.2.6.3) the resulting estimated CQG was £43,000, £37,000 and £31,000 for donepezil, galantamine and rivastigmine, respectively.
- 4.2.6.5 For the responder analyses, the clinical effectiveness estimates reported by the MRC Biostatistics Unit (see sections 4.1.2.11, 4.1.3.9 and 4.1.4.10) were used in the Assessment Group model that included the assumptions used for the augmented base case. Non-responders on the drug were assumed to incur drug costs (allowing for dose titration as per Summary of Product Characteristics) and monitoring costs for the first 6 months.
- 4.2.6.6 In view of the loss of randomisation consequent on studying responder benefit, three different methods of interpretation were modelled for the estimates of clinical effectiveness in the responder analysis. The first assumed that the non-responders, when taken off the drug, incur the same costs and benefits as all those on placebo. In the second method, the costs and benefits for all four treatment arms (responders and non-responders on the drug and on placebo) were calculated using the individual estimates of clinical effectiveness. Finally, the third method focused on the extra effect of responders on the drug over and above responders on placebo.

- 4.2.6.7 When modelled using the Assessment Group economic model the three methods resulted in CQG estimates for donepezil ranging from £21,000 to £60,000, depending on the method and the inclusion of carer benefits and behavioural symptoms in the augmented base case. For galantamine and rivastigmine the equivalent results were £25,000 to £76,000 and £5,000 to £55,000, respectively.
- 4.2.6.8 In modelling the subgroups based on cognitive impairment the clinical effectiveness data as synthesised by the MRC Biostatistics Unit were used (see sections 4.1.2.12, 4.1.3.10 and 4.1.4.11) in the SHTAC economic model. In order to be consistent with the augmented base case the pre-full-time care health state was assigned a utility that was representative of the subgroup under consideration (0.60). Using the MMSE definition for the moderate subgroup (10–20) the resulting estimates of CQG for donepezil were £39,000 to £46,000 depending on the inclusion of carer benefits and behavioural symptoms in the augmented base case. For galantamine and rivastigmine the equivalent results were £32,000 to £40,000 and £23,000 to £30,000, respectively. When the results of the meta-analysis for the subgroup of people with moderate Alzheimer's disease as performed by the MRC Biostatistics Unit were included (–3.98 [99% CI –4.74 to –3.22] for moderate and –5.44 [99% CI –6.94 to –3.94] for moderately severe), the resulting estimates of CQG for donepezil ranged from £31,000 to £38,000, depending on the inclusion of carer benefits and behavioural symptoms in the augmented base case, and from £32,000 to £35,000 for galantamine and from £20,000 to £26,000 for rivastigmine. Using the results of the meta-analysis by the MRC Biostatistics Unit for the subgroup of people with mild Alzheimer's disease (–1.86 [99% CI –2.89 to –0.83]), the resulting estimates of CQG for donepezil ranged from £61,000 to £80,000, depending on the inclusion of carer benefits and behavioural symptoms in the augmented base case, and from £56,000 to £76,000 for galantamine and from £47,000 to £62,000 for rivastigmine.

Moderately severe to severe Alzheimer's disease

4.2.7 Memantine

- 4.2.7.1 Five economic evaluations were found for memantine in people with moderately severe to severe Alzheimer's disease; three were in abstract or poster form, and the other two were in press. One of the five evaluations related to the UK. All suggested that memantine was more effective and less costly compared with no treatment. The Assessment Group used the manufacturer's model for memantine for moderately severe to severe Alzheimer's disease for their economic analysis, by changing some of the assumptions in the model.
- 4.2.7.2 In the probabilistic model submitted by the manufacturer, disease states were described by severity, level of dependency (dependent or independent), whether people were in institutional care or not and death. The people in the model made transitions between the states. The time horizon was 2 years. The transition probabilities between health states (defined as categories of MMSE score) were derived from a single RCT of memantine monotherapy. The odds ratio associated with institutionalisation was also derived from this single RCT and was not adjusted for differences in disease severity. The manufacturer calculated from this model that memantine dominated placebo for the total population as well as the subgroups except the subgroup of severe and dependent people with Alzheimer's disease for which an estimate of approximately £4,000 was reported for the CQG.
- 4.2.7.3 The Assessment Group re-ran the model using a set of assumptions similar to those used in its own model for AChE inhibitors, and the CQG estimates were between £37,000 and £53,000. Further changes to transition probabilities in relation to the available trial evidence for, and costs of care associated with, memantine raised the estimated CQG in the manufacturer's model substantially above £53,000. In response to the

Assessment Report, the manufacturer recalculated its model using the majority of the alterations suggested by the Assessment Group and reported an estimated CQG of £23,000 for the base case and £48,000 for the scenario in which only the additional cost of memantine over 2 years was included. Estimates for the CQG of the subgroups of people with Alzheimer's disease who are moderately severe and (in)dependent ranged between £400 and £30,000 depending on a range of alternative assumptions including the odds ratio of dependency, odds ratio of institutionalisation and transition probabilities associated with disease severity and costs. The CQG estimates for the subgroup of severe and dependent were all above £100,000.

- 4.2.7.4 The manufacturer's submission after the request for extra analyses estimated the CQG for the moderately severe to severe group (the 'all patient scenario') to be between approximately £12,000 and £49,000 when memantine monotherapy was compared with no treatment depending on a range of alternative assumptions including the odds ratio of dependency, odds ratio of institutionalisation and transition probabilities associated with disease severity and costs.
- 4.2.7.5 At the request of the Institute the manufacturer also evaluated scenarios that related to patients who were classified as 'behaviourally disturbed', 'non-behaviourally disturbed' and 'behaviourally disturbed responders'. Estimates of the CQG for the behaviourally disturbed subgroup ranged from £9,000 to £35,000 depending on a range of alternative assumptions including the odds ratio of dependency, odds ratio of institutionalisation and transition probabilities associated with disease severity and utilities. The estimates of CQG for the subgroup of non-behaviourally disturbed ranged from £26,000 to £546,000 depending on a range of alternative assumptions including the odds ratio of dependency, odds ratio of institutionalisation and transition probabilities associated with disease severity and utilities. Identical one-way sensitivity analyses that were

restricted to include only 'behaviourally disturbed responders' reported estimates of CQG for memantine to a maximum of £23,000.

- 4.2.7.6 The manufacturer submitted a second economic evaluation, which compared the use of memantine in combination with donepezil against donepezil monotherapy. Most of the methods, results and accompanying discussion were marked commercial-in-confidence. The model suggests that memantine plus donepezil is more effective and less costly compared with 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, galantamine and rivastigmine) and memantine used in the treatment of people with Alzheimer's disease (sections 4.1 and 4.2). The Committee heard evidence on the nature of Alzheimer's disease and the use of these treatments from patients, carers and clinical experts.
- 4.3.2 The Committee was also mindful of the need to ensure that its advice took account of the efficient use of NHS/PSS resources.
- 4.3.3 The Committee also carefully considered comments received during consultation on the first Appraisal Consultation Document issued in March 2005, the consultation on the extra analyses issued in November 2005 and the consultation on the second Appraisal Consultation Document issued in January 2006.

Acetylcholinesterase inhibitors: donepezil, galantamine and rivastigmine

- 4.3.4 The Committee heard that since TA no. 19 was issued in 2001, the evidence base relating to the use of the AChE inhibitors has matured and continues to demonstrate that, compared with placebo, the AChE inhibitors provide small but consistent gains in scores on cognitive and global scales for people with mild to moderately severe Alzheimer's disease. The Committee noted,

however, that the evidence available on the long-term effectiveness of the AChE inhibitors on outcomes, such as quality of life and delayed time to nursing home placement, was limited and largely inconclusive.

4.3.5 The Committee heard that TA no. 19 has brought about an improved package of care for people with dementia in the form of more expert assessments, memory clinics and regular follow-up.

4.3.6 The Committee carefully examined the cost-effectiveness models provided by the Assessment Group and the manufacturers, and it noted the substantial differences in cost-effectiveness estimates between the manufacturers' models and those of the Assessment Group. The Committee noted that the Assessment Group considered that the manufacturers' cost-effectiveness calculations needed to be treated with considerable caution because:

- optimistic assumptions on estimates of mortality and costs were used,

and it also noted that:

- disease progression models were based on cognition states alone (donepezil and rivastigmine)
- transition probabilities were derived from an open-label study (rivastigmine)
- long cycle lengths were included (donepezil)
- long time horizons were included (galantamine).

4.3.7 The Committee considered that the Assessment Group's model formed the most appropriate basis for exploring cost effectiveness because it focused on health states that represent outcomes of importance in Alzheimer's disease, and used more realistic inputs on costs compared with the manufacturers' models. It also allowed for all three AChE inhibitors to be considered within a single framework. However, the Committee recognised that the base case findings from the Assessment Group model needed further exploration (see 4.3.10 below).

- 4.3.8 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 usually be considered appropriate for the NHS.
- 4.3.9 After hearing testimony from clinical and patient experts, the Committee considered a number of issues that might alter the estimates of the cost effectiveness of the AChE inhibitors from the base case presented by the Assessment Group. At the Committee's request the NICE secretariat provided an augmented base case (derived from the Assessment Group's model but amended by the secretariat) with additional sensitivity analyses for consideration by the Committee (section 4.2.6).
- 4.3.10 The Committee carefully discussed the range of considerations, raised in the consultation, that could change the cost effectiveness of the AChE inhibitors obtained by the Assessment Group's base-case model and those of the augmented base case that was formulated as a result of the extra analyses by the secretariat (see sections 4.2.5 and 4.2.6). These considerations (taking together the elements of the augmented base case and the points raised in consultation) included the following.
- 4.3.10.1 *The benefits and utility estimates for people with Alzheimer's disease.* A number of considerations that might suggest a higher utility gain than that of the base case were discussed. The Committee remained convinced that inclusion of a higher utility estimate (0.69) for all people in pre-full-time care, the inclusion of the benefits that accrue to people who do not reach full-time care in the time-frame of the model, and the inclusion of the benefits to individuals who die before reaching full-time care were acceptable amendments to the base case. All of these considerations contributed substantially to the more favourable CQG estimates of the augmented base case. In response to the consultation on the first Appraisal Consultation Document, the Committee further discussed consultees' comments on the health-state utilities used to calculate the

benefits of the AChE inhibitors in the economic analysis. However, the Committee was mindful of the fact that the augmented base case now already included a substantial increase in the benefit of using AChE inhibitors from the estimates given in the Assessment Group's base case (see section 4.2.6.1). The Assessment Group's base case was associated with an average QALY gain of 0.032 to 0.035 and this gain increased to an average of 0.06 in the augmented base case. The Committee noted that this gain in QALYs was of the same order of magnitude as that in the economic analyses published in the literature and submitted by manufacturers. The Committee was not persuaded that these average QALY gains could reasonably be increased further.

4.3.10.2 *Benefits to carers.* The Committee carefully considered to what extent it was reasonable to ascribe utility gains to carers of people with Alzheimer's disease being treated with AChE inhibitors. Comments received during consultation highlighted the positive impact that treatment with AChE inhibitors had on the quality of life of carers. However, quantitative evidence on the impact of AChE inhibitors on carer benefits in the form of utilities is lacking. The Committee considered that although at any point in time a carer may have a higher utility if they were caring for a person responding to drug treatment than if the person were not on the drug or not responding to the drug, the effect of the drug would be to delay progression of the condition, in which case the carer would still be faced at some time in the future with the same difficulties caused by disease progression. Exceptions could be if the person did not progress to later and more difficult stages of the disease within 5 years or because of death. On this basis, the Committee decided that it was reasonable to add to the modelling of the augmented base case a utility benefit of 0.01 for carers (see also section 4.2.6.3). It noted that the new estimates of cost effectiveness would then be in the range of £36,000 to £50,000 per QALY gained.

- 4.3.10.3 *Carer costs*. Having concluded that the incorporation of carer benefits in the economic modelling in the form of utilities was appropriate, the Committee also discussed whether carer costs should be included in the economic model. The Committee agreed that when the effect on carers is to be considered in an economic evaluation, it should only be incorporated as 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 because of the potential for double counting. In addition the Committee noted that the relevant NICE guidance on performing economic evaluations (National Institute for Clinical Excellence (2001); *Guide for manufacturers and sponsors*) states that 'the evaluation should be conducted from the perspective of the NHS and PSS decision-maker. That is to say, the benefits should include all clinical and health-related benefits valued from the perspective of society, and costing should include all use of NHS and PSS resources required to achieve those benefits'. The Committee therefore concluded that it would not be appropriate to include carer costs in the augmented base case or sensitivity analyses on the augmented base case.
- 4.3.10.4 *Behavioural symptoms in Alzheimer's disease*. The Committee heard from clinical and patient experts during consultation that benefits arising from the amelioration of behavioural disturbances as a result of the use of AChE inhibitors should be taken into consideration in the economic analysis. The Committee also considered the potentially greater need for the AChE inhibitors given the non-availability of certain antipsychotics for the behavioural symptoms associated with dementia. On balance, the Committee decided that it would be appropriate to include an effect of AChE inhibitors on behavioural symptoms associated with dementia, but it was not convinced that inclusion of an element of harm in the economic analysis from further prescribing of antipsychotics as a result of their recommendations was appropriate. A one-way sensitivity analysis on the augmented base case plus the element for carer benefits (see section

4.3.10.2), was associated with cost-effectiveness estimates ranging from £31,000 to £43,000 per QALY gained.

4.3.10.5 *Mortality.* In response to the comments from consultees on the first Appraisal Consultation Document the Committee considered the inclusion of the original risk equation for mortality from the AHEAD model in the augmented base case of the economic model. The Committee was mindful of the fact that the Assessment Group used a constant mortality rate irrespective of age and severity, although it is generally understood that there is a relationship between mortality and these factors. However, the Committee was not convinced that the Assessment Group's mortality estimate overestimated true mortality in the early years of the model. The Committee considered that the original AHEAD risk equation used mortality rates in the early years of the model too low to represent a population with mild to moderately severe Alzheimer's disease.

4.3.10.6 *Costs.* Although the Committee acknowledged that there is a paucity of good information on the costs for people with Alzheimer's disease treated with AChE inhibitors in the community, it concluded that the suggestion made in the consultation on the first Appraisal Consultation Document to use only those cost estimates of a recent study among people aged 65 years or older living in inner London (in which fewer than 10% were diagnosed with dementia) was not appropriate. In discussing the suggestion made in consultation that the costs of full-time care could be higher than used in the model, the Committee felt that the average of a range of published estimates would be more plausible. The Committee accepted the cost estimates used in the augmented base case having noted that, by including an average of cost estimates from a number of sources, it accepted more favourable estimates for both of the health states than those used by the Assessment Group. The Committee also concluded that including the proportion of the cost of nursing/residential care that is met by people with Alzheimer's disease (estimated as 30% by the Assessment Group) would not be appropriate as these costs are not

part of the NHS/PSS budget and therefore including them would not be consistent with NICE technology appraisal methods.

4.3.10.7 *Incorporating the responder definition of the NICE guidance of 2001 (TA no. 19).* From the consultation on the first Appraisal Consultation Document, the Committee was prompted to further consider a scenario in which extra benefits might be assumed for the subgroup of initial responders to treatment. If initial response was a reliable predictor of greater overall response to treatment, it would have a favourable impact on the estimates of CQG for the AChE inhibitors. The Committee reviewed evidence from current practice in England and Wales and the clinical evidence presented by the manufacturers for the responder analyses. It noted that both 'responders' on the AChE inhibitors and on placebo had apparent cognition gains at 6 months. The Committee carefully considered the wide range of cost-effectiveness estimates resulting from modelling the various approaches to the interpretation of this evidence and concluded that the translation of gains in clinical effectiveness into a cost-effective strategy was unconvincing. The Committee specifically heard and accepted that such retrospective responder analyses could plausibly lead to significant selection bias and related uncertainty in the interpretation of the resulting estimates of clinical effectiveness. Overall, the Committee was not persuaded that the responder definition used in TA no. 19, when applied to the results of the pivotal randomised clinical trials, would lead to a cost-effective use of the AChE inhibitors in the NHS.

4.3.10.8 *Subgroups of people with Alzheimer's disease.* The Committee heard from clinical and patient experts that some people with Alzheimer's disease benefit considerably more from the AChE inhibitors than others, when the results of treatment are analysed retrospectively. It therefore considered whether it might be possible to define, prospectively, subgroups of people with Alzheimer's disease who might benefit more than average, and for whom AChE inhibitors might be a relatively cost-effective treatment. The Committee was not initially provided with any evidence, either from the

experts or patient level data from RCTs that could have identified this subgroup prospectively. It was mindful, however, of the possibility that the analysis of individual patient data from existing trials could conceivably identify a pragmatically valid subgroup that could reliably be recognised. In subsequently considering the extra analyses by the manufacturers and reported upon by the MRC Biostatistics Unit the Committee was persuaded that the clinical effectiveness data for the subgroup analyses based on severity of cognitive impairment (see sections 4.1.2.12, 4.1.3.10 and 4.1.4.11) would not suffer from selection bias to the same extent as those for the responder analyses. The Committee understood that focusing on specific subgroups based on severity of cognitive impairment is clinically plausible when considering treating people with Alzheimer's disease. In accepting the subgroup analyses using severity of cognitive impairment, the Committee reviewed the estimates of cost effectiveness. It noted that for people with moderate Alzheimer's disease these estimates ranged from £23,000 to £35,000 depending on the choice of AChE inhibitor and by including carer benefits in the augmented base case. Conversely, the Committee noted that for the subgroup of people with mild Alzheimer's disease estimates of cost effectiveness ranged from £56,000 to £72,000 depending on the choice of AChE inhibitor and by including carer benefits in the augmented base case. The Committee further discussed points raised in consultation focusing on the exclusion of people with mild Alzheimer's disease from its preliminary recommendations. These included suggestions that the cognitive benefits for mild patients were of greater value than similar gains in moderate patients (partly because of suggested ceiling effects in the MMSE scale), and also that there might be cumulative benefits from treating early. The Committee considered these points carefully but concluded that the absence of reliable evidence for either, taken together with the high incremental cost-effectiveness ratios seen for the mild group, did not support the case for extending treatment to mild cases.

4.3.11 The Committee also noted there was evidence that might indicate the cost-effectiveness estimates of the AChE inhibitors could be less favourable than the augmented base case (and even less favourable than the base case originally indicated in the Assessment Report). The Committee noted that the Assessment Group's meta-analysis of the effect of donepezil on ADAS-cog, and therefore its cost-effectiveness estimate, would have been less favourable if the results from the studies included had been restricted to their longer term (24-week) results, or if the results from the UK study (AD2000) had been included, or both.

4.3.12 The Committee considered the acquisition costs, the range of clinical effectiveness estimates, the different side-effect profiles and the results from direct comparisons between the AChE inhibitors. It concluded that it would not be appropriate to differentiate between the drugs on the basis of their effectiveness, but in the light of its responsibility to take account of the effective use of NHS resources, the Committee considered that it was appropriate to indicate that prescribers should take into account the acquisition costs of each AChE inhibitor when considering which of the AChE inhibitors to prescribe as well as other factors pertinent to the choice of an individual AChE inhibitor such as adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions, and dosing profiles.

4.3.13 In considering the comments from consultation that suggested an individualised approach to the use of cognition scores for the initiation of AChE inhibitors, the Committee accepted that for specific groups of people with Alzheimer's disease, such as those with learning disabilities or with marked language problems MMSE scores are difficult to interpret. However, the Committee concluded that these groups were not disadvantaged by the treatment entry level of MMSE. The discontinuation level of MMSE is set by the AChE inhibitor licence. It considered that the interests of learning disability patients were best served by including initiation of treatment by learning disability specialists in the guidance.

4.3.14 Having considered all the evidence and the comments of consultees, the Committee concluded that the resulting estimates of cost effectiveness could be considered sufficiently acceptable to suggest that the prescribing of AChE inhibitors for people with Alzheimer's disease and moderate cognitive impairment (MMSE scores between 10 and 20) is cost effective.

Memantine

4.3.15 For moderately severe to severe Alzheimer's disease, the Committee considered evidence from three trials of memantine (including evidence from one trial that was submitted after the Assessment Report was completed). The results from pooled analyses of these data were also considered, as were the results from a fourth RCT in which a subgroup comprised patients with moderately severe to severe Alzheimer's disease. The Committee also took into account the submitted economic evidence.

4.3.16 The Committee noted that for the two memantine monotherapy trials (in which the majority of patients had Alzheimer's disease) the results were inconsistent, with the late submission of a trial having statistically non-significant results on all scales. Although data from the pooled analysis of these two memantine monotherapy RCTs and a pooled analysis of the three RCTs versus placebo showed statistically significant advantages (at the 95% level) on a number of outcomes the absolute magnitude of difference on all outcomes was modest.

4.3.17 Analyses were also presented for a subgroup of participants with signs of agitation/aggression, delusions or hallucinations (known for the purposes of this document as the 'behaviourally disturbed' subgroup) and for patients classified as behaviourally disturbed who were also considered to have responded to treatment. The Committee noted the advice from the MRC Biostatistics Unit that the treatment effect for the group of behaviourally disturbed people did not differ sufficiently from that of the group of non-behaviourally disturbed people, so that these two groups could not be

considered as distinct subgroups for the purposes of considering the effectiveness or cost effectiveness of treatment. The Committee also considered the method used by the manufacturer for categorising people as behaviourally disturbed. It was neither specific enough nor consistent with the definition proposed by other consultees in consultation on the second Appraisal Consultation Document.

4.3.18 Overall, considering the published and unpublished evidence, the Committee concluded that the evidence to determine the clinical effectiveness of memantine in either the whole population of moderately-severe to severe Alzheimer's disease or the subgroup of people with behavioural symptoms was currently insufficient. Nevertheless, irrespective of this conclusion, the Committee sought to consider the cost-effectiveness calculations that might be derived from these limited data.

4.3.19 The Committee had a number of concerns regarding the values and assumptions made within the manufacturer's original economic model such as the MMSE transition probabilities, ADCS-ADL scores associated with dependency and whether or not people became institutionalised.

4.3.20 For changes in disease severity (incorporated into the model as changes in category of MMSE health state), large differences in proportions were included in the analysis when changes in MMSE as reported from one of the RCTs showed very small differences in disease progression as measured using this outcome. For example, in the 'all patient scenario', the mean overall difference in disease progression in MMSE, as recorded by one RCT, was less than 1 between the two treatment groups. However, in this scenario an average of 22% and 45% of patients who received memantine and no treatment, respectively, progressed from moderately severe to severe disease at the end of one (Markov) cycle.

4.3.21 The Committee also noted that the MMSE-based transition probabilities had only been derived from one of the two RCTs of memantine monotherapy.

Although MMSE was not recorded in the second trial, it noted that the results of one of the monotherapy RCTs were generally less favourable than the other monotherapy RCT. The Committee concluded therefore that the current MMSE transition probabilities were likely to overestimate the cost-effectiveness of memantine.

4.3.22 The Committee also noted that the odds ratio associated with institutionalisation was also based on the single and more favourable (towards memantine) of the two RCTs. It also noted that in the derivation of this variable, the odds ratio had not been adjusted for disease severity (therefore leading to the high probability of double counting treatment effects) and was based on seven events (that is, the analysis was based on seven people being institutionalised during the trial). The Committee therefore concluded that the evidence to support the assertion that memantine prevents patients with moderately severe to severe Alzheimer's disease from being institutionalised was currently insufficient.

4.3.23 The Committee noted that the odds ratio associated with dependency was based on the results from both RCTs of memantine monotherapy. However, too few details of how this ratio was constructed were provided for the Committee to reasonably establish its validity. It was unclear as to how 'dependency' had been measured within the trial. The Committee also questioned the plausibility of the odds ratios for the various patient groups given the overall negligible differences in outcomes reported by the RCTs (mean values ranged between 1.3 and 9.5 depending on the patient group under analysis).

4.3.24 The Committee noted that setting the odds ratios for dependency and institutionalisation to 1 (effectively removing these variables from the analysis) produced estimates of CQG between approximately £70,000 to £90,000 depending on the patient group or subgroup under consideration. It also noted qualitatively that factoring in less favourable changes in disease severity from the second RCT would further increase these estimates of CQG.

4.3.25 The Committee therefore concluded that on the basis of current evidence on clinical effectiveness memantine could not reasonably be considered a cost-effective therapy for moderately severe to severe Alzheimer's disease.

5 Recommendations for further research

5.1 Research is required 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 people with moderately severe to severe Alzheimer's disease with memantine.

5.2 Research is required, preferably using RCTs, to investigate the effect of memantine on subgroups of people with Alzheimer's disease suggested to derive enhanced benefit from memantine, such as those with behavioural disturbance.

5.3 Research is required to assess the relationship between disease progression of people with Alzheimer's disease and carer utility (quality of life).

6 Implementation

6.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

6.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare

organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

- 6.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).

[Note: tools will be available when the final guidance is issued]

- *Costing report and costing template* to estimate the savings and costs associated with implementation.
- *Audit criteria* to monitor local practice (see appendix C).

7 Related guidance

- 7.1 NICE is in the process of producing the following clinical guideline.

Dementia: the treatment and care of people with dementia in health and social care. Clinical guideline. NICE in collaboration with Social Care Institute for Excellence (SCIE). (Publication expected February 2007.)

8 Proposed date for review of guidance

- 8.1 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.
- 8.2 The guidance on this technology will be considered for review in September 2009.

Andrew Stevens
Chair, Appraisal Committee
May 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both 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 Jane Adam

Radiologist, St George's Hospital, London

Professor 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 (Vice Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice,
University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital,
Blackpool

Professor Christopher Eccleston

Director Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor Terry Feest

Professor of Clinical Nephrology, Southmead Hospital

Ms Alison Forbes

Lay Member

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital, Oxford

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 Senior Lecturer in Primary Care Medicine, Alyth Health Centre, Angus, Scotland

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Lay Member

Professor Philip Routledge

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

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

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, & Associate Professor, 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

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

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 and Alastair Fischer

Technical Analysts, NICE project team

Alec Miners

Technical Advisor, NICE project team (until December 2005)

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.

Loveman E, Green C, Kirby J, et al. *The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine, and memantine for Alzheimer's disease*, August 2004. Including erratum 2004 and amendment 2005.

The first additional analysis was prepared by the NICE secretariat.

Boysen M, Fischer A and Miners A, *Extra work on appraisal of drugs for Alzheimer's disease. Technical Report no. 1* (January 2005).

Data on the use of the drugs in a clinical setting received from formal Consultees, practitioners who have been involved in such data collection and from people with a known interest in such data sets who have responded to the public consultation via the NICE website. (May 2005)

The second additional analysis was prepared by the NICE secretariat following submissions by the manufacturers (see under B below) and validation of these submissions by the MRC Biostatistics Unit.

Matthews F, *Review of memantine submission, and detailed investigation of submissions for donepezil, rivastigmine and galantamine including new analysis* (November 2005), and *additional submission information* (November 2005) and *correction on memantine analyses* (December 2005).

Boysen M, Fisher A and Miners A, *Donepezil, rivastigmine, galantamine (review) and memantine for the treatment of Alzheimer's disease. Technical Report no. 2* (November 2005) and *Addendum* (December 2005).

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the first and second Appraisal Consultation Documents. Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors (original submissions in September/October 2004 and subsequent submissions in October/November 2005):

- Eisai Ltd
- Lundbeck Ltd
- Novartis Pharmaceuticals UK Ltd
- Shire Pharmaceuticals Ltd

II Professional/specialist and patient/carer group:

- Age Concern England
- Alzheimer's Society
- Counsel and Care for the Elderly
- Dementia Care Trust
- Mental Health Foundation
- Association of British Neurologists
- British Geriatrics Society
- British Neuropsychiatry Association
- For Dementia
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Psychiatrists
- Royal Pharmaceutical Society
- Cheshire West PCT
- Department of Health
- Leeds West PCT
- Rugby PCT

- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- National Collaborating Centre for Chronic Conditions
- National Public Health Service for Wales
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- 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 donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the first and second Appraisal Consultation Documents.

- Mrs Louise Chambers, Chief Executive, Dementia Care Trust
- Mrs Carol O'Connor, patient expert, nominated by the Alzheimer's Society
- Professor John T O'Brien, Professor, Old Age Psychiatry, Wolfson Research Centre, Newcastle General Hospital
- Mr Mervyn Richardson, patient expert, nominated by the Alzheimer's Society
- Mr Gordon Wilcock, Professor, Care of the Elderly, University of Bristol

- Dr David Wilkinson, Consultant in Old Age Psychiatry, Memory Assessment and Research Centre, Morgreen Hospital, Southampton
- Professor Roy W Jones, Director, The Research Institute for the Care of the Elderly, St Martins Hospital, Bath

Appendix C. Detail on criteria for audit of the use of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease

Possible objectives for an audit

An audit could be carried out to ensure that donepezil, galantamine, rivastigmine and memantine are used appropriately in the treatment of Alzheimer's disease.

Possible patients to be included in the audit

An audit could be carried out on people referred to specialists in the care of people with dementia (that is, a psychiatrist, including one specialising in learning disability, a neurologist or a physician specialising in the care of the elderly) for dementia or suspected dementia in a reasonable time period for audit, for example 6 months to 1 year.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of the appropriateness of use of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. A person with Alzheimer’s disease of moderate severity is offered donepezil, galantamine and rivastigmine as management options only after all the following circumstances are met:</p> <p>a. Only a specialist initiates treatment and</p> <p>b. The views of the person’s carer/s on the person’s condition are sought and</p> <p>c. The person who is taking donepezil, galantamine or rivastigmine is reviewed every 6 months by an appropriate specialist team to include the following:</p> <p>I. MMSE score and</p> <p>II. Global, functional and behavioural assessment</p>	<p>100% of people with moderate Alzheimer’s disease for whom 1a and 1b are met</p>	<p>A. A person with mild Alzheimer’s disease who is receiving donepezil, galantamine or rivastigmine at the time of publication of this guidance and is continued on therapy until he or she or his or her carers and/or specialist consider it appropriate to stop</p> <p>B. For 1c, there is a locally agreed protocol for shared care that provides for assessment consistent with 1c</p>	<p>A person with Alzheimer’s disease of moderate severity has a Mini Mental State Examination (MMSE) score of between 10 and 20 points. Clinicians will need to agree locally on how the offer of drug treatment is documented, for audit purposes. A ‘specialist’ in the care of people with dementia means a psychiatrist, including one specialising in learning disability, a neurologist or a physician specialising in the care of the elderly. ‘Global assessment’ can include the clinician’s interview-based impression of change (CIBIC) and CIBIC-plus for global outcomes. Tests for functional assessment include the Progressive Deterioration Scale (PDS) for functional/quality-of-life scales. Clinicians will need to agree locally on how carer views are documented, what constitutes global, functional and behavioural assessment and how</p>

			the findings of assessment are documented, for audit purposes.
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<p>2. A prescription for donepezil, galantamine or rivastigmine is continued only in the following circumstances:</p> <p>a. The person's MMSE score remains at or above 10 points and</p> <p>b. The person's global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect and</p> <p>c. The views of the person's carer/s on the person's condition at follow-up are sought</p>	<p>100% of people for whom a prescription for donepezil, galantamine or rivastigmine is continued for the treatment of Alzheimer's disease</p>	<p>None</p>	<p>When the MMSE score falls below 10 points, the person would not normally be prescribed any of these three drugs. See above for an explanation of assessment of global, functional and behavioural condition. Clinicians will need to agree locally on how the determination that the drug is considered to be having a worthwhile effect, how the carer/s' views are documented and the acceptable interval in weeks for 6 monthly reviews, for audit purposes.</p>
<p>3. When the decision has been made to prescribe donepezil, galantamine or rivastigmine, therapy is initiated with the drug with the lowest acquisition cost</p>	<p>100% of initial prescriptions for donepezil, galantamine or rivastigmine</p>	<p>A. An alternative drug is prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions, and dosing profiles</p>	<p>'Acquisition cost' takes into account required daily dose, price per dose once shared care has started. 'Shared care' refers to an agreed protocol between a specialist and GPs who may be managing the continuing care of the person taking donepezil, galantamine or rivastigmine. Clinicians will need to agree locally on the lowest acquisition cost and how other considerations listed in the exception are</p>

			documented, for audit purposes.
4. Memantine is prescribed for a person Alzheimer's disease	0% of people with Alzheimer's disease	A. A person with Alzheimer's disease who is receiving memantine as part of a clinical trial at the time of publication of this guidance and is continued on therapy including after the conclusion of a clinical trial until he or she or her or her carers and/or specialist consider it appropriate to stop	A clinical trial is well designed.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **excep**tion listed}{\text{Number of patients to whom the **meas**ure applies} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.