National Institute for Health and Clinical Excellence

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

Includes a review of NICE technology appraisal guidance 19

NICE technology appraisal guidance 111 (amended)

NICE technology appraisal guidance 111 (amended September 2007, August 2009)
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Ordering information

You can download the following documents from www.nice.org.uk/TA111

- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- 'Understanding NICE guidance' – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1328 (quick reference guide)
- N1329 ('Understanding NICE guidance').

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NOTE: This technology appraisal was first issued in November 2006. It was amended in September 2007. This second amendment is effective from August 2009.

1 Guidance

This guidance applies to donepezil, galantamine, rivastigmine and memantine within the marketing authorisations held for each drug at the time of this appraisal; that is:

- donepezil, galantamine, rivastigmine for mild to moderately severe Alzheimer's disease
- memantine for moderately severe to severe Alzheimer's disease.

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 patients with Alzheimer's disease of moderate severity only (that is, subject to section 1.2 below, 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 patients 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 (subject to section 1.2 below) 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.

When using the MMSE to diagnose moderate Alzheimer's disease, clinicians should be mindful of the need to secure equality of access to treatment for patients from different ethnic groups (in particular those from different cultural backgrounds) and patients with disabilities.

1.2 In determining whether a patient has Alzheimer's disease of moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:

- where the MMSE is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties **or**
- where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case.

In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of moderate severity by making use of another appropriate method of assessment. For the

avoidance of any doubt, the acetylcholinesterase inhibitors are recommended as options in the management of people assessed on this basis as having Alzheimer's disease of moderate severity.

The same approach should apply in determining for the purposes of section 1.1 above, and in the context of a decision whether to continue the use of the drug, whether the severity of the patient's dementia has increased to a level which in the general population of Alzheimer's disease patients would be marked by an MMSE score below 10 points.

1.3 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 comorbidity, possibility of drug interactions and dosing profiles.

1.4 Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.

1.5 Patients with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and patients with moderately severe to severe 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 MMSE (30 points) for cognitive outcomes. MMSE score, for example, denotes the severity of cognitive impairment as follows:

- mild Alzheimer's disease: MMSE 21–26
- moderate Alzheimer's disease: MMSE 10–20
- moderately severe Alzheimer's disease: MMSE 10–14
- 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 (NICE technology appraisal guidance 19) 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) 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). 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) 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 16–24 mg daily. Prices are £68.32 for 28 modified-release capsules of 16 mg (given once daily) and 56 tablets of 8 mg (given twice daily) and £84.00 for 28 modified-release capsules of 24 mg and 56 tablets of 12 mg (excluding VAT; BNF 50th edition). 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) is an AChE 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). 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) 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). This equates to £899.59 per year of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.7 In clinical trials in mild to severe dementia, involving patients treated with memantine and patients treated with placebo, the most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were dizziness, headache, constipation and somnolence. These adverse events were usually of mild to moderate severity. For full details of side effects and contraindications, see the summary of product characteristics.

4 Evidence and interpretation

The Appraisal Committee 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 specialists. It also took into account 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 clinical global impression of change (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 all 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 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 15–20; 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 10–14; 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 NICE technology appraisal guidance 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 NICE technology appraisal guidance 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 Seven 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. (NICE technology appraisal guidance 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 2294) no statistical significance was noted between treatment groups and placebo.

4.1.3.4 The results of five 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 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 NICE technology appraisal guidance 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 10–20; 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 10–14; 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 than those on placebo withdrew because of adverse events. Retrospective responder analyses using the NICE technology appraisal guidance 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. (NICE technology appraisal guidance 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 NICE technology appraisal guidance 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 10–20; 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 10–14; 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 NICE technology appraisal guidance 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. (NICE technology appraisal guidance 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. 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 end point (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 [± donepezil] versus placebo [± 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 cluster scores (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 [± donepezil] versus placebo [± 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. 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). Compared with all those on placebo, the differences in proportions of patients responding on memantine were 17.4% (NPI-cluster), 23.9% (ADCS-ADL19) and 27.8% (SIB). 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 end point 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 all three RCTs.

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 NICE

as described in technical report numbers 1, 2 and their addenda. Following the judicial review, the executable model was released to consultees who were asked to comment on its reliability to inform the Committee's recommendations.

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 10 were of treatment of people with mild to moderate Alzheimer's disease. In 5 (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 USA, 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 (ICERs); 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 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 section 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 £5000 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 Southampton Health Technology Assessments Centre (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.

4.2.7 Consultee comments on executable model

4.2.7.1 The Alzheimer's Society commented that the probabilistic sensitivity analysis in the SHTAC model included variables whose values were unknown and also variables whose values were known for any one person but which were subject to variation between people (for example, age, sex and ADAS-cog score). The Alzheimer's Society amended the model to incorporate subgroups of people based on age (70, 75, 80 years) and ADAS-cog score (21, 12.5, 4). The Alzheimer's Society also considered that in clinical practice people who were not considered to be responding to treatment would stop treatment and therefore the model should consider only those people who responded to treatment. The Alzheimer's Society amended the model to include the costs of identifying responders and increased the efficacy of the technologies to include a mean reduction in ADAS-cog of 5.12 to reflect that responders had on average a larger benefit from treatment.

4.2.7.2 The Alzheimer's Society commented on the appropriateness of a number of parameter values and amended these in the SHTAC model. These included the proportions of people treated in the community, the costs of full-time care, the utility of a person with mild disease prior to entering full-time care and the drop in utility associated with a person entering full-time care. The Alzheimer's Society noted that the cost implication to carers should be included in the economic model. The Alzheimer's Society also noted that the augmented benefit had been incorrectly implemented in the model by multiplying the number of people who remained out of full-time care during the 5-year span in the non-treatment arm. The Alzheimer's Society commented that this was incorrect and that the benefit should be applied to the difference between the number of people that avoid full-time care in the non-treatment arm and the number of people that avoid full-time care in the treatment arm. Finally the Alzheimer's Society noted that a costs cell in the model

did not update automatically when the inputs were changed, and that the value had to be entered manually in the appropriate cell. The Alzheimer's Society did not indicate that this had led to an error in the model.

4.2.7.3 The Alzheimer's Society undertook a cumulative analysis of the amendments detailed in their comments, excluding age and ADAS-cog score from the probabilistic sensitivity analysis. ICERs are presented for each subgroup based on age (70, 75, 80 years) and ADAS-cog score (21, 12.5, 4). For a subgroup of people age 75 years and with an ADAS-cog score of 12.5, they presented a revised base-case ICER of £14,500 per QALY gained. This figure included their responder analysis, 15% of people in full-time care treated in the community, annual full-time care costs of £21,651, a utility estimate for a person in pre-full-time care of 0.83 and the inclusion of a cost to carers of £1495 per year.

4.2.7.4 The British Geriatrics Society did not amend the economic model. Their comments included questions about the exclusion of the responder analysis and the effect on estimates of cost effectiveness of using a cohort model which they considered may not take into account individual variation among people. In addition, they asked about the inclusion of mortality in the model and the source of the time horizon over which modelling had been completed. Finally, the British Geriatrics Society asked whether competing risks, treatment persistence and compliance had been taken into account in the model.

4.2.7.5 Eisai made a number of comments about the reliability of the economic model and made several amendments. Eisai also raised a number of issues about the ease of use of the model, including labelling of cells, cells not updating automatically so that changes were not propagated through the model, inputs read from multiple locations, inputs zeroed out and the exclusion of fixed random seeds which meant that results for each analysis could not be

exactly replicated. Eisai noted that these issues made establishing the reliability of the model challenging. Eisai attempted to replicate the results in the NICE technical reports and amended the model to produce a new base-case ICER of £56,216 per QALY gained. This estimate included a starting age of 75 instead of 74 years and the inclusion of behavioural symptoms in the economic model. An ICER of £45,120 per QALY gained was also presented for mild disease using a responder analysis, which included the two assumptions above. Subsequent amendments to the model made by Eisai were based on their revised base case and responder analysis.

4.2.7.6 Eisai identified six technical errors with the model. The following five issues were subject to exploratory amendments to the executable model.

- The death index (that is, the probability of death) for older people had been applied to younger people and vice versa and an age of 72 rather than 73 years had been used to select the index.
- Hazards had been applied as though they were probabilities.
- The probability of death for people in pre-full-time care had used the probability of death for people in full-time care and vice versa.
- The selection of the full-time care index calculation (that is, the probability of entering full-time care) had been set to age 74 instead of 73 years.
- Discounting of costs had been applied incorrectly.

The cumulative impact of making these changes was to reduce the ICER for donepezil from their base-case of £56,216 per QALY gained to £54,453 per QALY gained. An ICER of £43,559 per QALY gained was reported for the responder analysis. The sixth issue identified by Eisai related to the sampling of patient characteristics. Eisai highlighted that the probabilistic sensitivity analysis included variables whose values were unknown (for

example, treatment effect) and also variables whose values were known but subject to variation between people (for example, age). They also commented that some variables were not subject to variation (for example, treatment effect on behavioural symptoms) and others were varied over arbitrary ranges. In addition, Eisai commented that unit costs were varied in the probabilistic sensitivity analysis when it was more appropriate to vary frequency of resource use. Eisai did not amend the model in regard to this sixth issue and noted that the extent of the problems with sampling meant that it was not possible to identify the effect on the ICERs.

4.2.7.7 Eisai also included a series of sensitivity analyses to explore the impact on the ICER of using different assumptions and parameter estimates in the model:

- The assumption of constant mortality was removed by applying the death index to calculate the probability of death.
- The benefit to carers was increased from 0.01 to 0.02.
- The costs in the pre-full-time care and full-time care state were increased by 10%.
- The percentage of people in full-time care not living in the community was increased from 48% to 60%.
- The benefit in terms of ADAS-cog was increased by 0.5 to account for benefits in treatment between months 6 and 12.
- The effect of treatment on behavioural symptoms was increased from a 20% reduction to a 25% reduction.
- Monitoring of treatment was assumed to incur the cost of a general practitioner visit and not an outpatient visit.
- The utility of a person in full-time care was reduced from 0.34 to 0.3.

The cumulative impact of these changes was to reduce the ICER for donepezil from £54,453 to £31,603 per QALY gained. The ICER for the responder analysis was reduced to £23,128 per QALY

gained, or £30,633 per QALY gained if it was assumed that 30% of non-responders continued treatment.

4.2.7.8 Eisai highlighted a number of concerns which they did not amend in the economic model.

- The time horizon of 5 years was insufficient to capture the benefits for people with mild disease or for responders to treatment. The augmented benefit does not resolve the limitations of the time horizon.
- The model assigns a single health utility for pre-full-time care, which negates any benefits afforded by treatment over the period of time in which a person is in pre-full-time care.
- No half-cycle correction had been applied to the model for transitions and for discounting.
- The appraisal used discount rates of 1.5% for benefits and 6% for costs and not 3.5% for both benefits and costs.
- People with mild disease were assumed to have the same characteristics as people with moderate disease, including utility score, except for ADAS-cog score.
- The model assumed the effect of treating an average person with an average response and an average time to entering full-time care and ignored variability in response.
- The costs of caring for a person prior to entering full-time care were assumed to be the same regardless of disease severity.
- The equations used to predict time to full-time care included categorical variables that require presence or absence, but these are applied in the model as proportions.
- The responder and discontinuation analyses generated illogical results.
- The utility for a person with mild disease prior to entering full-time care was not revised from the utility for a person with moderate disease.

- Discounting of deterministic results and augmented benefit was applied incorrectly.
- The duration of symptomatic disease prior to starting treatment was inappropriately assumed to be 1 year.

4.2.7.9 The Research Institute for the Care of the Elderly (RICE) did not make amendments to the economic model, but raised a number of issues about the model and commented on the likely impact of these on the ICERs. RICE commented that the model was a cohort model that had included an average person who had an average response to treatment. RICE considered that this would lead to over-estimation of the ICERs and ignored variation in treatment response among patients. RICE commented that the effect of treatment should be analysed as a function of baseline cognitive status and applied individually to each patient. RICE also commented that the model had assumed a constant mortality, which it considered would also lead to over-estimation of the ICERs. RICE also noted that the model should consider the impact on the ICERs of stopping treatment in those people who did not show a response. Finally RICE stated that it was important to perform cumulative analyses as well as one-way sensitivity analyses.

4.2.7.10 Shire Pharmaceuticals identified a number of issues about the usability of the model, including the requirement for separate mild and moderate disease models, errors in the distributions around estimates and cells not updating automatically, which meant that changes to inputs were not propagated through the model. Shire commented on the probabilistic sensitivity analysis, which had included variables whose values were both unknown (for example, treatment effect) and variables whose values were known for any one person but which were subject to variation between people (for example, age). Shire amended the model to include subgroups of people based on age (65, 70, 75, 80 years) and ADAS-cog score

(21, 12.5 and 4). Shire noted that the formula used to select ADAS-cog score was invalid and included values outside of the range for moderate disease and did not include the full range for mild disease. However, with the inclusion of subgroups based on ADAS-cog score this no longer required amending in the model. Shire also stated that the model should include the benefits of treatment beyond 6 months and the continuation of treatment only for those people who showed a response. Shire considered that the estimates of cost data were inappropriate and amended the model to include a cost value for full-time care of £19,312 per year. Shire also commented that the utility of a patient before entering full-time care did not update to reflect a higher value for patients with mild rather than moderate Alzheimer's disease. Shire also noted that an assumption of constant mortality was inappropriate. They considered that this would overestimate mortality.

4.2.7.11 Shire undertook a cumulative analysis of a number of their amendments for each of the subgroups of people based on age (65, 70, 75 years) and ADAS-cog score (21, 12.5 and 4). ICERs were presented for each of these subgroups. For a subgroup of people age 75 years with an ADAS-cog of 12.5, Shire calculated an ICER of £13,000 per QALY gained. This included removal of the assumption of constant mortality by reducing the rate of mortality in the first 3 years, updated full-time care cost data and either stopping treatment in those who did not respond to treatment or assuming a continued benefit beyond 6 months. Shire considered that the additional benefit associated with either continuing treatment in only people who responded or providing additional benefit beyond 6 months was the same (that is, an additional benefit of 5.1 on the ADAS-cog score). Therefore the impact on the ICER of including either of these revised assumptions was the same.

4.2.8 Decision Support Unit report

4.2.8.1 The Decision Support Unit (DSU) evaluated the issues identified by consultees and considered that four issues were related to the economic model's technical reliability and required amending in the model. These were:

- implementing the hazard for transition to full-time care
- separating the characteristics of uncertainty and variability in the model
- implementing discounting
- implementing the augmented benefit.

Each of these issues was corrected in the model. In addition their cumulative impact was examined.

Hazard for transition to full-time care

4.2.8.2 The DSU considered that an instantaneous hazard rate for the transition to full-time care had been treated as a probability. For mild disease, correcting this changed the ICER from £63,749 to £63,164 per QALY gained (donepezil) and from £59,108 to £59,500 per QALY gained (galantamine). For moderate disease correcting this changed the ICER from £31,550 to £31,556 per QALY gained (donepezil).

Sampling of patient characteristics

4.2.8.3 The probabilistic sensitivity analysis included both variables that were intrinsically unknown for any patient and variables that were known but subject to variation. The DSU set all patient characteristics to their mean value, and created subgroups by ADAS-cog score and age at starting treatment. For mild disease treated with donepezil, the base-case ICER was £63,749 per QALY gained. Three age subgroups were created (64, 70 and 74 years) and the ICERs for each of these subgroups were £84,659, £73,804 and £55,779 per QALY gained, respectively. For mild disease treated with galantamine, the base-case ICER was £59,108 per

QALY gained. The ICERs for the age subgroups were £80,755, £69,856 and £51,978 per QALY gained, respectively. For moderate disease treated with donepezil, the base-case ICER was £31,550 per QALY gained. The ICERs for the three age subgroups 64, 70 and 74 years were £37,384, £43,480 and £30,999 per QALY gained, respectively.

Discounting

4.2.8.4 The DSU thought that the first 6 months of treatment had not been taken into account in the discounting of costs and benefits. The discounting had also been applied inconsistently for part of the QALY calculation. For mild disease, correcting this changed the ICER from £63,749 to £60,607 per QALY gained (donepezil) and from £59,108 to £57,941 per QALY gained (galantamine). For moderate disease, correcting this changed the ICER from £31,550 to £31,053 per QALY gained (donepezil).

Augmented benefit

4.2.8.5 The DSU considered that the SHTAC model gave benefit to patients in the treatment arm based on the number of patients in the non-treatment arm who remained out of full-time care during the 5-year time span of the model. The DSU amended the model so that the benefit was based on the number of patients who remained out of full-time care in the treatment arm. For mild disease, correcting this changed the ICER from £63,749 to £61,060 per QALY gained (donepezil) and from £59,108 to £56,866 per QALY gained (galantamine). For moderate disease, correcting this changed the ICER from £31,550 to £30,287 per QALY gained (donepezil).

Cumulative impact (DSU-amended base case)

4.2.8.6 The DSU cumulatively analysed the impact on the ICER of making all the changes for different subgroups of people based on age. For mild disease treated with donepezil, the augmented base-case ICER was £63,749 per QALY gained. The amended ICERs for the

three age subgroups (64, 70 and 74 years) were £77,464, £67,408 and £51,660 per QALY gained, respectively. For mild disease treated with galantamine, the augmented base-case ICER was £59,108 per QALY gained. The amended ICERs for the three age subgroups were £71,404, £63,916 and £48,574 per QALY gained, respectively. For moderate disease treated with donepezil, the augmented base-case ICER was £31,550 per QALY gained. The amended ICERs for the three age subgroups were £36,334, £41,041 and £28,561 per QALY gained, respectively.

4.2.8.7 In addition, the DSU cumulatively analysed the impact on the ICER of making the changes but using a weighted average of the costs and QALYs for the three age subgroups. For mild disease treated with donepezil, this reduced the augmented base-case ICER from £63,749 to £58,133 per QALY gained. For mild disease treated with galantamine, this reduced the augmented base-case ICER from £59,108 to £54,662 per QALY gained.

Additional sensitivity analyses performed by the DSU

4.2.8.8 The DSU conducted three further sensitivity analyses to explore issues raised by consultees. These analyses were completed using the ICERs that included the corrections made by the DSU (that is, the DSU-amended base case).

4.2.8.9 Carer benefits were added to the treatment arm of the model and not to people who did not have full-time care in the non-treatment arm of the model. Section 4.3.10.2 discusses the Committee's consideration about the inclusion of carer benefits. It was not clear to the DSU whether it was the Committee's intention for the carer benefit to be only included in the treatment arm. Therefore it was difficult for them to determine whether this was a reliability issue. The DSU modelled the impact of added utility for patients in both arms who, in the model, did not go on to receive full-time care. This led to a small change in the ICERs. For example, for mild disease the DSU-amended base-case ICERs ranged from £49,000 to

£77,000 per QALY gained depending on age and treatment, but with the inclusion of carer benefits in both arms the ICERs ranged from £48,000 to £76,000 per QALY gained. The ICER for moderate disease treated with donepezil changed from the DSU-amended base case of between £29,000 and £41,000 per QALY gained to between £30,000 and £41,000 per QALY gained, depending on age.

4.2.8.10 The prevalence of 30% behavioural symptoms and 20% reduction in these symptoms was included in the model for moderate Alzheimer's disease but was not included in the model for mild Alzheimer's disease. When this change was incorporated in the mild disease model the ICERs were reduced by between £5000 and £10,000 per QALY gained, although they all remained in excess of £43,000 per QALY gained.

4.2.8.11 The utility score for pre-full-time care was based on an ADAS-cog score of 24 (which equates to moderate disease). Consultees commented that there should have been different utility scores for pre-full-time care in the mild and moderate disease models. The DSU updated the model with a new utility score based on the mapping equations used in the original economic model. The DSU noted that the utilities generated by the equation may overestimate the utility score for a person with Alzheimer's disease because some of the utility scores were higher than those for an otherwise healthy population. The use of the revised utility scores reduced the ICER (from the DSU-amended base case) for mild disease by between £5000 and £10,000 per QALY gained and increased the ICER for moderate disease by £5000 to £7000 per QALY gained. For example, for mild disease the DSU-amended base-case ICER ranged from £49,000 to £77,000 per QALY gained, depending on age and treatment, but using different utility scores the ICERs ranged from £42,000 to £64,000 per QALY gained. The ICER for moderate disease treated with donepezil changed from the DSU-

amended base case of between £29,000 and £41,000 per QALY gained to between £30,000 and £41,000 per QALY gained depending on age.

Moderately severe to severe Alzheimer's disease

4.2.9 Memantine

4.2.9.1 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.

4.2.9.2 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 £4000 was reported for the CQG.

4.2.9.3 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.

4.2.9.4 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.

4.2.9.5 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 £9000 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.

4.2.9.6 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 specialists. The Committee was mindful of the need to ensure that its advice took account of the cost-effective use of NHS/PSS resources.

4.3.2 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.

4.3.3 Following the judicial review outcome in May 2008, the Committee considered the comments received from consultees after release of the executable economic model that informed NICE technology

appraisal guidance 111, a report by the DSU reviewing these comments and consultees' responses to the DSU report.

Acetylcholinesterase inhibitors: donepezil, galantamine and rivastigmine

4.3.4 The Committee heard that since NICE technology appraisal guidance 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 NICE technology appraisal guidance 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 section 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 specialists 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 specialists 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 (NICE technology appraisal guidance 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 NICE technology appraisal guidance 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 specialists 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 robust 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 ICERs 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 or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties, the use of MMSE scores is not always appropriate as a means of assessing the severity of dementia. The Committee felt that learning disability specialists were best placed to judge entry and continuation criteria for people with learning disabilities that could be considered equivalent to the general Alzheimer's population. Following the judgement of the High Court on 10 August 2007, this guidance has been amended at sections 1.1 and 1.2 above to set out more clearly the approach which should be applied in relation to

patients with learning disabilities and other relevant groups of people.

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.

4.3.15 Following the Court of Appeal ruling of May 2008 the Appraisal Committee carefully discussed the individual comments received from consultees after consideration of the executable economic model, the DSU report reviewing those comments and consultees' response to the DSU report. These considerations (taking together the points raised in consultation) included the following.

General issues with the economic model

4.3.16 The Committee considered the comment from consultees that suggested that the time horizon of 5 years chosen for the economic model did not capture all benefits, particularly for an assessment of mild disease or of responders to treatment, and that the augmented benefit used by the Committee did not appropriately resolve this issue. The Committee considered that there was nothing intrinsically inappropriate with a 5-year model in dementia care and that two of the manufacturer's models had also used a 5-year time horizon. However, the Committee had recognised from early on in the appraisal that the original SHTAC model without any amendments could miss benefits accruing to patients with a slower disease trajectory. The Committee noted that this was the problem that the augmented base case addressed. The Committee was satisfied that inclusion of the augmented benefit had resulted in almost a doubling of the average QALY gain per patient to 0.06 from the original Assessment Group results (see section 4.3.10.1). Moreover, the Committee reviewed the graphical depiction of the

probability of people remaining in pre-full-time care resulting from the Assessment Group model, and noted that the capacity to benefit was greatest in the second, third and fourth year after starting the AChE inhibitors, and that at year 5 the difference between patients using AChE inhibitors and no treatment was diminishing. Therefore extending the time horizon instead of adding the augmentation would not exceed the benefits allocated in the augmented base case. The Committee further noted that the structural assumptions around the time horizon of the economic model had been commented on during the original consideration of the evidence base, before the release of the fully executable version of the model. The Committee also noted that no results of exploratory analyses were presented by consultees. The Committee concluded that it was satisfied that the augmented base case provided extra benefits that might not have been captured by a 5-year time horizon, and remained persuaded that the average QALY gains could not reasonably be increased further.

4.3.17 The Committee reviewed comments that half-cycle corrections should have been applied to event transitions and to the discounting of costs and benefits. The Committee noted that the consultee indicated that without a half-cycle correction, costs and benefits occurring through the year would only be accumulated at the end of a year. The Committee heard from the DSU that the cycle length in the model was 1 month, and that they would not expect application of a half-cycle correction to event transitions to make a material difference to the ICERs for either mild or moderate Alzheimer's disease. The Committee also considered the impact of applying a half-cycle correction to discounting the costs and benefits in the model. The Committee noted that when explored by SHTAC in the original assessment report, the application of no discounting in the model resulted in minimal changes to the results. The Committee understood that a similar impact was to be expected from the augmented base case of the mild and moderate

patient groups. The Committee therefore accepted that applying a half-cycle correction to the augmented base case for the mild and moderate patient groups would result in minimal changes to the results.

4.3.18 The Committee noted the comments from a consultee related to the fact that discounting in the economic model uses values of 1.5% for benefits and 6% for costs when it is now formally determined that 3.5% should be used for both. The Committee acknowledged that the latter values for discounting were now part of the updated reference case for the methods of technology appraisals, but at the time the evidence was collected for this appraisal the former values were used. The Committee noted that the original assessment report showed that when the new discount rates were included in sensitivity analysis the ICERs increased.

Coding used in the economic model

4.3.19 The Committee discussed the issues raised by consultees that focused on the coding of the economic model. It accepted that a coding error was made in the executable model in which a mean value of 75 years was used for the age of the patient cohort instead of 74 years as referred to in the assessment report. The Committee noted that, when explored by the DSU, the correction resulted in minimal changes to the reported ICERs.

4.3.20 The Committee considered the consultees' comments about the implementation of the augmented and carer benefits in the economic model. The Committee accepted that the benefits should have been applied to the number of patients who remained out of full-time care in the treatment arm and not to the number of patients who remained out of full-time care in the non-treatment arm. The Committee considered the DSU exploration and accepted that the resulting ICERs from this amendment were approximately £61,000 and £57,000 per QALY gained for patients with mild Alzheimer's disease treated with donepezil and galantamine, respectively.

4.3.21 The Committee then considered comments about which group of patients should have received the augmented and carer benefits in the economic model. The Committee confirmed that its intention had been that these benefits should only be applied to the treatment group in the model (see section 4.2.6.1) and not to both groups as the benefits reflect that AChE inhibitors could give rise to an improvement in cognition that would not be accounted for in the SHTAC model structure for patients who did not move to full-time care. Therefore, the Committee did not accept the DSU sensitivity analysis that included applying carer benefits to both arms of the model.

4.3.22 The Committee considered comments concerning the application of the death index in the economic model. The Committee noted the comment that the death index for patients in pre-full-time care was applied to patients in full-time care and vice versa. The Committee accepted that the application of the death index in the model was incorrect. The Committee noted that it would not have any impact on the reported ICERs for patients with mild or moderate Alzheimer's disease because, for calculating those ICERs, a constant proportional hazard was used which was not dependent on the index included in the model. In addition, the Committee noted further comments on the use of the death index, including using the index for older patients to apply to younger patients, and vice versa, and the use of an age of 72 years to select the index instead of 73 years. The Committee noted that the correction by the consultee of the latter two errors had led to small increases in the ICERs. The Committee noted that the ICERs upon which the guidance was based assumed a constant proportional hazard and were not dependent on the value of the death index included in the model.

4.3.23 The Committee noted the reduction in the ICERs reported by consultees when the selection of the full-time care index calculation

was set to 73 instead of 74 years. The Committee accepted that this needed to be amended and noted that when this was corrected by a consultee it had led to a reduction in the ICER of approximately £1500.

Handling of variables in the economic model

4.3.24 The Committee accepted comments from consultees that noted that the model calculates the transition to full-time care as a hazard but subsequently applies this as if it was a probability. The Committee noted the DSU's correction of this and accepted that this resulted in minimal changes to the ICERs for the population of people with mild Alzheimer's disease.

4.3.25 The Committee accepted the methodological comment from consultees that the model conflates heterogeneity in the patient population with uncertainty by including in the probabilistic sensitivity analysis values which are intrinsically known for each patient, but subject to variation (for example, age). The Committee noted both the consultees' and the DSU's explorations of this issue in subdividing the patient population by age and cognition and concluded that the consultee and DSU age stratification (but see 4.3.26) of people with mild Alzheimer's disease did not result in the generation of ICERs within the normally accepted range, without making further changes to parameter estimates. The Committee further heard from the DSU that other exploratory analyses of the model using alternative approaches to separating variability from parameter uncertainty (for example, using a weighted average of the costs and QALYs for the different age groups or separating out the sampling of patient characteristics from the sampling of parameter uncertainty) had led to similar estimates of the ICER as those in the augmented base case. Overall, the Committee was not persuaded that the sampling of patient characteristics had led to an overestimation of the ICERs. In addition, the Committee considered that there was no evidence of differential effectiveness of the AChE

inhibitors in patients of different ages, and that exploration of subgroups on the basis of age requires robust evidence for differential effectiveness or differences in baseline risk for other key parameters and outcomes before being considered further.

4.3.26 The Committee recognised that the model assumed the effect of treating an average patient who had an average response and a resulting average time to entering full-time care. In addition the Committee recognised that the baseline characteristics of a patient with mild Alzheimer's disease were assumed to be the same as for a person with moderate Alzheimer's disease, except for ADAS-cog score. The Committee discussed that the former was a general feature of cohort models. Cohort models explore variation in patient characteristics through subgroup analysis and by the use of probabilistic sensitivity analysis. Both probabilistic sensitivity analysis and subgroup analysis had been undertaken in this appraisal, including for the most plausible subgroup, defined by starting cognition. The Committee noted that evidence submitted by the manufacturers and analysed by the MRC Biostatistics Unit had shown a clear differentiation in response between subgroups of varying cognition and not for others such as age or the presence or absence of behavioural symptoms. Overall the Committee felt that the use of a cohort modelling approach, with exploration of uncertainty and variation in patient characteristics through the use of probabilistic sensitivity analysis and subgroup analysis where appropriate was reasonable. In addition, the Committee considered that no evidence had been presented for differential patient characteristics for subgroups of patients related to starting cognition but that in its acceptance of these subgroups it had accepted using the means and uncertainty chosen for the probabilistic sensitivity analyses. It noted that further exploration of the effect of such differences would require robust evidence collection and synthesis before being considered further. The Committee was mindful of the fact that such exploration will have

an effect on both subgroups of patients with moderate and mild Alzheimer's disease. The Committee concluded that the most appropriate process for consideration of new evidence and changes to key model assumptions would be a formal review of the guidance.

4.3.27 The Committee noted comments from consultees about how uncertainty had been captured in the probabilistic sensitivity analysis. The Committee noted that the consultees considered that not all variables subject to uncertainty had been varied and that others had been varied over arbitrary ranges. In addition, cost data had been varied rather than the frequency of resource use. The Committee heard from the DSU that the original assessment report had accurately reported which variables had been subject to variation and the ranges over which they had been varied. The DSU did not therefore consider that these were reliability issues for the model. The Committee noted that the sources of the parameters had been given in the assessment report and that this had been subject to consultation and review by the Committee. In addition the Committee considered that costs, utility, monitoring and behavioural symptoms had been subject to one-way sensitivity analyses. The Committee considered that incorporating more variables in the probabilistic sensitivity analysis and wider ranges of distribution would be likely to increase rather than decrease uncertainty around the ICER value.

4.3.28 The Committee considered the comment from consultees about the implementation of categorical variables in the economic model. For example, that the equations used to predict time to full-time care are based on the presence or absence of behavioural symptoms, yet the model applies these data as though patients have a 'proportion of symptoms'. The Committee noted that consultees had not provided any quantification of the impact on the ICER. The Committee accepted the view of the DSU that although the

indicator variables such as those used for sex were binary, the expected value for a cohort of patients can be calculated by treating these as proportions.

4.3.29 Within the context of the handling of variables in the model, the Committee discussed comments from a consultee about the way discounting was implemented in the economic model. These comments were that the first 1.5 years had not been discounted, that in deterministic analyses the cumulative 5-year time in each state was discounted for the entire 5 years and that the discounting of the augmented benefit was applied inconsistently. The Committee accepted the comment that the model should have discounted the first 1.5 years and noted the consultees and DSU amendments to that effect resulted in small changes to the ICERs. The Committee heard that other comments focusing on discounting were the result of differences in interpretation of formulae used in the model, or when changed resulted in only small changes to the ICERs.

Assumptions used in the economic model

4.3.30 The Committee considered the comments made by consultees about assumptions in the economic model that, in general, focused on the characteristics of the cohort in the model, the benefits of treatment with AChE inhibitors and costs. The Committee noted that these issues had been presented previously by consultees and had been discussed extensively by the Committee and explored at the appeal hearing. The Committee concluded that that the availability of, and comments on, the executable economic model did not change their previous considerations on these matters.

4.3.31 The Committee was aware that for some of the proposed changes, evidence was presented that post-dated the deadline for evidence collection for the original assessment report and/or extra work and could not be considered in the context of their consideration of comments on the executable version of the model. The Committee

indicated that estimates of parameter values would need to be subject to systematic identification and review of this new evidence before considering amendments proposed for model parameters. The Committee did not accept the consequences of comments related to assumptions about the duration of symptomatic disease before starting treatment, the benefit of treatment beyond 6 months, the benefits to carers, the costs of caring for people with Alzheimer's disease before they entered full-time care, the cost of full-time care, the mortality rate, the proportion of people with Alzheimer's disease treated in the community, costs of monitoring treatment, treatment persistence and compliance, particular distributions used and the health state utilities associated with mild and moderate Alzheimer's disease during full-time care. The Committee concluded that the most appropriate process for consideration of new evidence and changes to key model assumptions would be a formal review of the guidance.

4.3.32 The Committee discussed the consultee comments about utility values and the corresponding DSU sensitivity analyses. The Committee did not accept that the health state utilities for pre-full-time care should be included as a function of the individual starting value for cognition based only on the fact that such an exploratory relationship was used for the calculation of the augmented benefit. However, it did accept that considering that it had changed the pre-full-time care utility for the moderate subgroup, it would have been appropriate to consider a change to this utility for when the mild subgroup was considered. The Committee noted, however, that for the calculation of the augmented base case a utility range was used that stretched over the whole range of the ADAS-cog scale. This had the effect that implausibly high utilities were attributed to people with mild Alzheimer's disease in the pre-full-time care health state than would be expected for a person of the same age who did not have Alzheimer's disease. The Committee therefore did not accept the exact ICERs presented in the sensitivity analyses from

the DSU (carried out following consultees' comments that the utility for a person with mild Alzheimer's disease not in full-time care should be revised). The Committee agreed that it could be plausible to use a different starting utility than the one originally used for the subgroup of people with mild disease, but that the impact of such a change should be less than the results presented in the sensitivity analyses from the DSU. It concluded that a reasonable amendment to the utility in pre-full-time care would not result in the generation of ICERs within the normally accepted range for the subgroup of patients with mild Alzheimer's disease. The Committee noted comments that the model assigned a single utility to the pre-full-time care health state, which was suggested to negate any benefits from treatment over the pre-full-time care period. The Committee considered that assigning a single utility for the whole time in which a person is in the pre-full-time care health state, would be favourable to the cost effectiveness of the technology when compared with an alternative approach where the utility for a person in pre-full-time care is assumed to follow, for example, a relationship with cognition over time. Therefore, the Committee did not accept this suggestion. The Committee considered that exploration of other evidence for the relationship between health-related quality of life and health states in the economic model would need to be undertaken in a full review of the guidance.

4.3.33 The Committee noted the results presented by the DSU that addressed the comments from consultees that although written documentation indicated that behavioural symptoms had been included in the model for mild Alzheimer's disease, the actual model that was released included no analyses exploring behavioural symptoms and the effect of the AChE inhibitors on these symptoms. The Committee accepted that such a sensitivity analysis would be expected for the purpose of consistency. However, the Committee was mindful of the fact that the sensitivity

analysis including behavioural symptoms for the whole cohort and for the moderate dementia group used high values for both prevalence and drug effectiveness in reducing such symptoms. The Committee considered that these prevalence levels could be less plausibly applied to mild dementia than moderate dementia. Therefore, it did not consider that such an analysis in the model for mild Alzheimer's disease was appropriate clinically. The Committee considered that exploration of the evidence would need to be undertaken in a full review of the guidance.

4.3.34 Comments that requested the inclusion of carer costs as well as carer benefits were not considered in further detail by the Committee. The Committee remained convinced 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 was mindful that, for performing economic evaluations, the 'Guidance for manufacturers and sponsors' (2001) states that 'The evaluation should be conducted from the perspective of the NHS and Personal Social Service (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 in the augmented base case (see section 4.3.10.3).

4.3.35 Comments on the use of the responder analyses in the economic model were not discussed further by the Committee because of its previous conclusion that the clinical effectiveness data that had

informed such analyses were subject to significant selection bias and related uncertainty in their interpretation (see section 4.3.10.7).

4.3.36 The Committee noted that applying a discontinuation rule in the model for patients with mild Alzheimer's disease would not result in a difference in the estimates of cost effectiveness for these patients. It accepted that this was the result of using a specific annual rate of decline in cognition, and that this rate combined with the starting cognition level of people with mild disease, and the time horizon of the model would not result in people being considered for stopping treatment. The Committee further noted that when a discontinuation rule was included for the patient group with moderate Alzheimer's disease this had not resulted in significantly different estimates of cost effectiveness. The Committee considered that exploration of other evidence for implementation of a stopping rule would need to be undertaken in a full review of the guidance.

Summary

4.3.37 In summary, the Committee concluded that there were a number of technical inaccuracies in the model that required exploration. The Committee accepted the amendments proposed by the DSU, as well as the amendment of the starting age of the full-time care index. The Committee did not consider that it was appropriate to present subgroups of people based on age. The Committee concluded that the cumulative impact of the changes it considered appropriate reduced the base-case ICER for mild Alzheimer's disease to approximately £55,000 to £58,000 per QALY gained (for galantamine and donepezil, respectively) which is further reduced by approximately £1500 when using the appropriate starting age of the full-time care index. The Committee noted the sensitivity analyses on estimates of health-related utility performed by the DSU but did not consider that the results of these were appropriate to consider as base-case estimates of the ICERs for the AChE

inhibitors. It accepted that the ICERs could be lower than the base case but concluded that the amendments had not reduced the ICERs for the subgroup of people with mild Alzheimer's disease to within the range normally accepted as a cost-effective use of NHS resources.

4.3.38 The Committee considered that comments on changes to parameter values based on evidence that it had not reviewed previously would be most appropriately dealt with through a formal review of the guidance. The Committee considered that the comments from consultees highlighting new evidence on the parameter estimates indicated that a review of the guidance was appropriate.

Memantine

4.3.39 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.

4.3.40 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.

4.3.41 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 approach used by the manufacturer for categorising people as behaviourally disturbed. The Committee took the view that it was neither specific enough nor consistent with other definitions.

4.3.42 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.

4.3.43 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.

4.3.44 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.

4.3.45 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.

4.3.46 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.

4.3.47 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).

4.3.48 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 and £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.

4.3.49 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 Implementation

5.1 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.

5.2 '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.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA111).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 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.

6.2 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.

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

7 Related NICE guidance

Published

- Dementia: supporting people with dementia and their carers in health and social care. NICE clinical guideline 42 (2006). NICE in collaboration with

Social Care Institute for Excellence (SCIE). Available from www.nice.org.uk/CG42

8 Review of guidance

8.1 A review of the guidance on this technology will begin when the amended guidance is published and at the earliest in September 2009.

Andrew Dillon
Chief Executive
August 2009

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 three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. 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.

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

Professor David Barnett (Vice-Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr Jane Adam
Department of Diagnostic Radiology, St George's Hospital

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

Mrs Elizabeth Brain
Lay Member

Professor Karl Claxton

Professor of Health Economics, University of York

Mrs Fiona Duncan

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

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Mr Mike Spencer

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

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

Dr Richard Cookson (until September 2007)

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

Professor Christopher Eccleston (until September 2007)

Director Pain Management Unit, University of Bath

Professor Terry Feest (until September 2007)

Professor of Clinical Nephrology, Southmead Hospital

Ms Alison Forbes (until September 2007)

Lay Member

Ms Linda Hands (until September 2007)

Consultant Surgeon, John Radcliffe Hospital, Oxford

Dr Elizabeth Haxby (until September 2007)

Lead Clinician in Clinical Risk Management, Royal Brompton Hospital

Dr Rowan Hillson (until September 2007)

Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson (until September 2007)

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

Dr Simon Mitchell (until September 2007)

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget (until September 2007)

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne (until September 2007)

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

Professor Philip Routledge (until September 2007)

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

Dr Stephen Saltissi (until September 2007)

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Debbie Stephenson (until September 2007)

Head of HTA Strategy, Eli Lilly and Company

Dr Cathryn Thomas (until September 2007)

General Practitioner and Associate Professor, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter (until September 2007)

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

Professor Mary Watkins (until September 2007)

Professor of Nursing, University of Plymouth

Dr David Winfield (until September 2007)

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

Dr Amanda Adler (from April 2009)

Consultant Physician, Cambridge University Hospitals Trust

Dr Robin Carlisle (from April 2009)

Deputy Director of Public Health, Rotherham PCT

Dr Simon Dixon (from April 2009)

Reader in Health Economics, University of Sheffield

Dr Richard Harling (from April 2009)

Director of Public Health, Worcestershire PCT and Worcestershire County Council

Dr Peter Heywood (from April 2009)

Consultant Neurologist, Frenchay Hospital

Professor Philip Home (from April 2009)

Professor of Diabetes Medicine, Newcastle University

Dr Vincent Kirkbride (from April 2009)

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Ian Lewin (from April 2009)

Consultant Endocrinologist, North Devon District Hospital

Dr Alec Miners (from April 2009)

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr James Moon (from April 2009)

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr David Newsham (from April 2009)

Lecturer (Orthoptics), University of Liverpool

Mrs Angela Schofield (from April 2009)

Chairman, Bournemouth and Poole Teaching PCT

Professor Iain Squire (from April 2009)

Consultant Physician, University Hospitals of Leicester

Mr David Thomson (from April 2009)

Lay Member

Mr William Turner (from April 2009)

Consultant Urologist, Addenbrooke's Hospital

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Eleanor Donegan
Technical Lead

Meindert Boysen and Alastair Fischer
Technical Leads (until September 2007)

Zoe Garrett
Technical Adviser

Alec Miners
Technical Adviser (until December 2005)

Bijal Joshi
Project Manager

Alana Miller
Project Manager (until September 2007)

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, 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, Fischer A, 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).

The Decision Support Unit (DSU) report for this appraisal was prepared by The School of Health and Related Research, The University of Sheffield.

- Longworth L and Allan W, Donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease: a review of comments submitted by consultees on the reliability of the economic model.

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 as well as the executable economic model. Consultee organisations are provided with the opportunity to appeal against the final appraisal determination. Organisations listed in I II and III also have the opportunity to appeal against the final appraisal determination.

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

- Eisai (plus comments on the executable model)
- Lundbeck Ltd
- Novartis Pharmaceuticals UK Ltd
- Shire Pharmaceuticals (plus comments on the executable model)

II Professional/specialist and patient/carer groups:

- Age Concern England
- Alzheimer's Society (plus comments on the executable model)
- British Geriatrics Society (plus comments on the executable model)
- 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

III Other consultees

- Cheshire West PCT
- Department of Health
- Leeds West PCT
- Rugby PCT
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and 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 (plus comments on the executable model)

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