NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA111.

This guidance is partially replaced by NG97.

1 Guidance

This guidance has been partially updated by the NICE guideline on dementia. See update information for more information.

1.1 The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified in 1.4 and in recommendation 1.5.5 of the NICE guideline on dementia.

1.2 Memantine monotherapy is recommended as an option for managing Alzheimer's disease for people with:

- moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors **or**
- severe Alzheimer's disease.

  Treatment should be under the conditions specified in recommendation 1.5.5 in the NICE guideline on dementia.

1.3 This recommendation has been updated and replaced by recommendation 1.5.5 in the NICE guideline on dementia.

1.4 If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the 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 AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

1.5 When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also 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.

1.6 When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:

- if the cognition score 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 difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education **or**
- if it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia **or**
- if there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia.

  In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.

2 Clinical need and practice

2.1 Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features.

2.2 Population data from 2005 indicate that 380,000 people have Alzheimer's disease in England and Wales. The UK incidence of Alzheimer's disease in people over the age of 65 years is estimated to be 4.9 per 1000 person-years. Between 50 and 64% of people with Alzheimer's disease are estimated to have mild to moderately severe disease, and approximately 50% have moderately severe to severe disease.

2.3 Alzheimer's disease is usually insidious in onset and develops slowly but steadily over several years. It predominantly affects older people. The median survival for people with Alzheimer's disease from onset has been estimated at 7 years, although survival figures vary and depend on how they are measured, comorbidities, age (median survival decreases with increasing age) and sex.

2.4 Progression is characterised by deterioration in cognition (for example, thinking, conceiving and reasoning), functional ability (for example, activities of daily living such as dressing, personal hygiene and handling money), behaviour (for example, agitation, wandering and uncharacteristic aggression) and non-cognitive symptoms including depression, delusions and hallucinations. People with Alzheimer's disease might find it increasingly difficult to do everyday activities, such as shopping, socialising and recognising people and places. Communication may become a problem as people find it more difficult to find words and remember names. In later stages of disease, physical problems can include problems with eating, swallowing, incontinence, and unsettled and unsettling behaviour. Alzheimer's disease may also be associated with loss of confidence and feelings of fear, confusion,

apathy, stigma and depression. The effects of Alzheimer's disease are heterogeneous and vary from patient to patient.

2.5 Alzheimer's disease has many impacts including physical, mental, nursing, medical and social impacts. Carers (including friends and family) are affected by the progressive deterioration in cognition, function and behaviour of a person with Alzheimer's disease. Behavioural symptoms can have a particular impact on carers, and are often the reason cited for a person with Alzheimer's disease going into full-time residential care. Alzheimer's disease can have a profound and far-reaching effect on family and carers as well as the patient including institutionalisation and a financial impact on family, carers and the state.

2.6 The severity of Alzheimer's disease can be assessed using several methods, depending on the setting (for example research or clinical practice) and the outcome being assessed. Clinical practice uses a variety of measures, often along with clinically based assessments such as biographical interview. Severity is frequently defined by Mini Mental State Examination (MMSE) score:

- 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.

2.7 The aims of treatment are to promote independence, maintain function and treat symptoms including cognitive, non-cognitive (hallucinations, delusions, anxiety, marked agitation and associated aggressive behaviour), behavioural and psychological symptoms.

2.8 There is no cure for Alzheimer's disease. Current management involves the treatment of cognitive, non-cognitive and behavioural symptoms. AChE inhibitors (donepezil, galantamine and rivastigmine) and memantine are the pharmacological treatments available specifically for Alzheimer's disease. Non-pharmacological treatment includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home

nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.

3 The technologies

Donepezil

3.1 Donepezil (Aricept, Eisai/Pfizer) is an AChE inhibitor, which works by increasing the concentration of acetylcholine at sites of neurotransmission. Donepezil has a marketing authorisation in the UK for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. It is given initially at 5 mg once daily at bedtime. After 1 month the treatment should be assessed, and the dose can be increased to a maximum of 10 mg once daily if necessary.

3.2 Common undesirable effects include diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia. For full details of side effects and contraindications, see the summaries of product characteristics.

3.3 Donepezil is available as tablets and orodispersible tablets. Net prices are stated. The cost of tablets is £59.85 (5 mg, 28-tablet pack) and £83.89 (10 mg, 28-tablet pack). The cost of orodispersible tablets is £59.85 (5 mg, 28-tablet pack) and £83.89 (10 mg, 28-tablet pack) ('British national formulary' [BNF] edition 60). Costs may vary in different settings because of negotiated procurement discounts.

Galantamine

3.4 Galantamine (Reminyl, Shire) is an AChE inhibitor, which works by increasing the concentration of acetylcholine at sites of neurotransmission and also modulates activity at nicotinic receptors. Galantamine has a marketing authorisation in the UK for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type. The formulation given most frequently is a capsule given initially at 8 mg once daily for 4 weeks and then increased to 16 mg once daily for at least 4 weeks. Maintenance treatment is 16–24 mg once daily depending on assessment of clinical benefit and tolerability. An older tablet formulation and a liquid preparation are also available to be given twice a

day, see the summaries of product characteristics for more information.

3.5 Common undesirable effects include nausea and vomiting. For full details of side effects and contraindications, see the summaries of product characteristics.

3.6 Galantamine is available as tablets, oral solution and capsules. Net prices are stated. The cost of tablets is £68.32 (8 mg, 56-tablet pack) and £84.00 (12 mg, 56-tablet pack). Oral solution (4 mg/ml, 100 ml) costs £120.00. Modified release capsules cost £51.88 (8 mg, 28-capsule pack), £64.90 (16 mg, 28-capsule pack) and £79.80 (24 mg, 28-capsule pack) (BNF edition 60). Costs may vary in different settings because of negotiated procurement discounts.

Rivastigmine

3.7 Rivastigmine (Exelon, Novartis) is an AChE inhibitor, which works by increasing the concentration of acetylcholine at sites of neurotransmission. Rivastigmine has a marketing authorisation in the UK for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. The dose is initially 1.5 mg twice daily and may be increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to tolerance up to a maximum dose of 6 mg twice daily. Alternatively rivastigmine patches are available, initially using a 4.6-mg patch per day. This can be increased to a 9.5-mg patch per day for at least 4 weeks. See the summary of product characteristics for further information on using patches.

3.8 Common undesirable effects are mainly gastrointestinal including nausea and vomiting. For full details of side effects and contraindications, see the summaries of product characteristics.

3.9 Rivastigmine is available as capsules, oral solution and patches. Net prices are stated. The cost of 1.5 mg rivastigmine capsules is £33.25 (28-capsule pack) and £66.51 (56-capsule pack); 3 mg capsules cost £33.25 (28-capsule pack) and £66.51 (56-capsule pack); 4.5 mg capsules cost £33.25 (28-capsule pack) and £66.51 (56-capsule pack); 6 mg capsules cost £33.25 (28-capsule pack) and £66.51 (56-capsule

pack). Oral solution costs £99.14 (2 mg/ml, 120 ml). Patches cost £77.97 (4.6 mg/24 hours, 30 patches) and £77.97 (9.5 mg/24 hours, 30 patches) (BNF edition 60). Costs may vary in different settings because of negotiated procurement discounts.

Memantine

3.10 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 has a marketing authorisation in the UK for the treatment of patients with moderate to severe Alzheimer's disease. Memantine is initially given as 5 mg once daily and then increased in steps of 5 mg at weekly intervals to a maximum of 20 mg daily.

3.11 Common undesirable effects are dizziness, headache, constipation, somnolence and hypertension. For full details of side effects and contraindications, see the summaries of product characteristics.

3.12 Memantine is available as tablets and oral drops. Net prices are stated. 10 mg memantine tablets cost £34.50 (28-tablet pack), £69.01 (56-tablet pack) and £138.01 (112-tablet pack). 20 mg tablets cost £69.01 (28-tablet pack). A treatment initiation pack (7 × 5 mg, 7 × 10 mg, 7 × 15 mg, and 7 × 20 mg tablets) costs £43.13. Oral drops (10 mg/g) cost £61.61 for 50 g and £123.23 for 100 g (BNF edition 60). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Committee considered evidence from the Assessment Group, submissions from the manufacturers of donepezil, galantamine and memantine, the Alzheimer's Society, the Royal College of Psychiatrists, the British Geriatrics Society, clinical specialists and patient experts.

4.1.2 The Assessment Group conducted a systematic review of randomised controlled trials published since 2004 and those included in 'Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended)' (NICE technology appraisal guidance 111). The Assessment Group reviewed the clinical effectiveness of donepezil, galantamine, rivastigmine and memantine in accordance with their marketing authorisations. For the population with mild Alzheimer's disease (defined as MMSE 21–26) the AChE inhibitors (donepezil, galantamine and rivastigmine) were compared with each other and with best supportive care (that is, without treatment with any AChE inhibitors or memantine). For the population with moderate Alzheimer's disease (MMSE 10–20) the AChE inhibitors and memantine were compared with each other and with best supportive care. For the population with severe Alzheimer's disease (MMSE less than 10) memantine was compared with best supportive care. The Assessment Group considered cognition, function, behaviour, global outcomes, mortality, institutionalisation, health-related quality of life and adverse effects. If possible, new evidence was pooled with the evidence from before 2004 using random effects meta-analysis compared with placebo. The effectiveness of treatments across different outcome measures was also explored in a pooled multiple outcome measure analysis to explore the characteristics of the evidence base. If data were sufficient, the Assessment Group pooled information on all technologies and their comparators in a mixed treatment comparison, using Bayesian Markov Chain Monte-Carlo

sampling.

4.1.3 The evidence on clinical effectiveness submitted by the three manufacturers included a wider selection of studies than was included by the definition of randomised controlled trials used by the Assessment Group in its evidence review. The manufacturer of donepezil conducted a systematic review of randomised controlled trials for donepezil since 2004, as well as presenting the evidence already included in NICE technology appraisal guidance 111. It also included a selected review of prospective longitudinal and observational studies. The manufacturer of galantamine submitted new data published since 2004, open-label studies and data from randomised controlled trials already submitted for NICE technology appraisal guidance 111, in 2004 or during the appraisal process. A search strategy with details of the inclusion and exclusion criteria was not submitted. The manufacturer of memantine submitted estimates of clinical effectiveness for the general population with moderate to severe Alzheimer's disease, and a subgroup of patients with agitation, aggression and/or psychotic symptoms. The manufacturer of memantine submitted a meta-analysis of six randomised controlled trials including individual patient data to allow categorisation into patients with moderate to severe disease and the subgroup with agitation, aggression and/or psychotic symptoms. Some of these trials were excluded by the Assessment Group because the trial populations included patients with mild disease, and individual patient data were not publicly available. The other submissions from consultees provided specific references to published literature on clinical effectiveness and were therefore covered by the Assessment Group's systematic review.

Mild to moderate Alzheimer's disease

Donepezil versus placebo

4.1.4 The Assessment Group included five new placebo-controlled comparisons of donepezil. The manufacturer of donepezil included new data from three randomised controlled trials, one subanalysis of a randomised controlled trial, two prospective longitudinal studies and three observational studies, six subgroup analyses and four meta-analyses (two systematic reviews and two pooled analyses), in addition

to data previously submitted.

4.1.5 For donepezil, the Assessment Group found no new studies reporting the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) at 12 or 24 weeks or MMSE at 12 weeks. The effectiveness estimates using these scales were therefore based on the studies included in NICE technology appraisal guidance 111. One new study was found that measured the effect of donepezil on cognition at 24 weeks follow-up. The overall pooled benefit using new and old data was significant on all scales (a mean change from baseline versus placebo of 1.165 [$p < 0.001$] and 1.206 [$p < 0.001$] at 12 and 24 weeks respectively using MMSE score, and −1.969 [$p = 0.006$] and −2.895 [$p < 0.001$] at 12 and 24 weeks respectively using ADAS-cog score) and the standardised mean difference of pooled outcomes increased with time for ADAS-cog. According to the manufacturer of donepezil, all 12 randomised controlled trials (from NICE technology appraisal guidance 111 and new submissions that reported on cognition using the ADAS-cog, MMSE or Severe Impairment Battery [SIB] scales) showed a statistically significant difference favouring donepezil versus placebo, with four of these reporting a statistically significant difference on two different cognitive scales.

4.1.6 One randomised controlled trial, described by the Assessment Group as being poorly reported, measured functional outcomes for donepezil. At 12 weeks follow-up, this trial showed a statistically significant benefit from donepezil (5 mg/day) for activities of daily living in an observed cases measured population. The heterogeneous collection of outcome measures prevented any quantitative synthesis of old and new evidence for individual measures since 2004. The pooled multiple outcome measure analysis for functional outcome data from the studies in NICE technology appraisal guidance 111 showed a statistically significant benefit for donepezil at all doses compared with placebo at 24 weeks - a mean change from baseline versus placebo of 0.298 ($p < 0.001$, no new data available). According to the manufacturer of donepezil, four randomised controlled trials showed a statistically significant difference favouring donepezil versus placebo on at least one scale and three reported non-significant trends in favour of donepezil. Additionally, the manufacturer cited a meta-analysis of seven randomised controlled trials

of donepezil reporting a statistically significant benefit favouring donepezil versus placebo.

4.1.7 None of the studies for donepezil newly identified by the Assessment Group provided additional data for behavioural function, so the results were based on studies included in NICE technology appraisal guidance 111, which noted no statistically significant benefit from donepezil compared with placebo at 12 or 24 weeks measured with the neuropsychiatric inventory (NPI). There were mean changes from baseline versus placebo of −2.249 ($p = 0.123$) and −3.116 ($p = 0.226$) at 12 and 24 weeks respectively using NPI. According to the manufacturer of donepezil, three randomised controlled trials found a statistically significant difference between donepezil and placebo in NPI score, with a fourth study finding a statistically significant difference for agitation or aggression but not total score. The manufacturer of donepezil also referred to six pooled studies that showed a statistically significant difference in favour of donepezil in NPI total score compared with placebo.

4.1.8 One of the new studies included by the Assessment Group measured global outcomes for donepezil and reported a statistically significant benefit on the clinical dementia rating (CDR). All of the evidence on the Clinician's Interview-Based Impression of Change (CIBIC)-plus was based on NICE technology appraisal guidance 111. A meta-analysis of the effectiveness of donepezil for the CIBIC-plus reported a statistically significant benefit of donepezil 10 mg/day compared with placebo at 12 and 24 weeks. The Assessment Group did not find any new studies that measured global outcomes at 24–26 weeks. The pooled multiple outcome measure analysis for the global outcome data from the studies in NICE technology appraisal guidance 111 showed a statistically significant benefit for donepezil at all doses compared with placebo at 24–26 weeks (a mean change from baseline versus placebo of −0.377 [$p < 0.001$] and −0.429 [$p < 0.001$] at 12 and 24 weeks respectively using CIBIC-plus score, and −0.263 [$p = 0.003$] and −0.568 [$p < 0.001$] at 12 and 24 weeks respectively using CDR score). According to the manufacturer of donepezil, global function (CIBIC-plus, CDR sum of boxes [CDR-SB] or the Gottfries, Brine and Steen scale [GBS]) was measured in nine of the studies presented in new and previous

submissions with statistically significant results in favour of donepezil in seven of them. A submitted meta-analysis of ten trials also showed significant improvement in global function compared with placebo using the CDR-SB.

4.1.9 According to the Assessment Group, none of the five newly identified studies for donepezil provided data on adverse events observed under randomised conditions except for limited data from one study. The manufacturer also presented safety data. In summary, the manufacturer of donepezil stated that new data since 2004 was consistent with that previously submitted.

4.1.10 The Assessment Group noted that none of the new randomised controlled trials included in the assessment report provided any additional data on quality of life, time to institutionalisation or mortality with donepezil.

4.1.11 The manufacturer of donepezil included prospective longitudinal and observational studies to support the view that cognitive benefits from donepezil are maintained for up to 3 years. The submission also included new data from a placebo-controlled trial of at least a 2-year duration and a subanalysis of a previous placebo-controlled study of 1 year duration. The manufacturer also presented evidence from randomised and non-randomised controlled trials to demonstrate that benefit was lost when treatment was stopped, the benefits of continuing treatment despite initial decline or stabilisation of MMSE, and the impact of improvement of neuropsychiatric symptoms on caregiver stress and burden.

4.1.12 The manufacturer of donepezil included evidence that patients showing clinical worsening may benefit from treatment compared with those on placebo or who were untreated. The manufacturer also included a responder analysis that showed how results varied depending on the definition of response. The manufacturer used these data to demonstrate the effects of treatment on carers.

4.1.13 A representative from the manufacturer of donepezil informed the Committee that an analysis of a single open-label study found an average of 17.5 months delay in the time to institutionalisation with

donepezil treatment. Survival data were not collected in any of the trials because follow-up periods were short and therefore there were few deaths during trials.

Galantamine versus placebo

4.1.14 The Assessment Group included three new randomised controlled trials of galantamine. The manufacturer of galantamine submitted data from before and after 2004 for six trials and four pooled analyses including mild, moderate and 'advanced moderate' subgroups.

4.1.15 All three studies included by the Assessment Group measured cognition and used ADAS-cog at various points between 6 and 26 weeks and showed improvement with galantamine compared with placebo. When the results of these were added to the results of NICE technology appraisal guidance 111, the pooled estimate demonstrated a statistically significant benefit of galantamine compared with placebo, which increased with time (mean changes from baseline versus placebo of −2.386 [$p < 0.001$] and −2.957 [$p < 0.001$] at 12–16 and 21–26 weeks respectively using ADAS-cog score). According to the manufacturer of galantamine, established randomised controlled trial data from five placebo-controlled trials in mild to moderate Alzheimer's disease showed statistically significant benefit in ADAS-cog score. This was reflected in the pooled data that included a subgroup of patients with additional cerebrovascular disease from a trial of patients with Alzheimer's disease (other patients in the trial had probable vascular dementia).

4.1.16 The Assessment Group found three new randomised controlled trials measuring functional outcomes for galantamine. The Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) data from the new trials were pooled with those of the studies found in 2004, and the overall pooled estimates showed statistically significant functional benefit from galantamine compared with placebo at 21–26 weeks (mean changes from baseline versus placebo of 1.394 [$p < 0.001$] and 2.234 [$p < 0.001$] at 12–13 and 21–26 weeks respectively). The results of Disability Assessment for Dementia (DAD) score were pooled at 21-26 weeks follow-up. Again this showed a statistically significant benefit of galantamine compared with placebo (mean changes from baseline

versus placebo of 3.761 [p < 0.001] at 21–26 weeks). Two new studies were added to the meta-analysis of combined functional outcome measures at 21–26 weeks. The pooled multiple outcome measure analysis showed a statistically significant functional benefit of galantamine compared with placebo. The manufacturer referred to four established placebo-controlled randomised controlled trials that showed benefits in terms of ADCS-ADL or DAD score, of which some were statistically significant, including the pooled data (which included a subgroup of patients with additional cerebrovascular disease from another trial).

4.1.17 Only one study included by the Assessment Group provided additional data for the effectiveness of galantamine in relieving behavioural symptoms, when compared with placebo. However, this did not show any statistically significant benefit. When the new data were pooled with previous data, at 13 weeks no significant benefit was found, but at 21–26 weeks the overall pooled estimate favoured galantamine significantly (mean changes from baseline versus placebo of −0.746 [p = 0.179] and −1.455 [p = 0.012] at 13 and 21–26 weeks respectively using NPI score). The manufacturer of galantamine referred to one study that showed statistically significant benefits in terms of NPI score, and another two placebo-controlled trials that showed non-significant benefits in terms of NPI score. Mixed results were reflected in the pooled data (including the subgroup of patients with additional cerebrovascular disease from another trial).

4.1.18 Two new studies found by the Assessment Group measured global outcomes for galantamine. One found a significant benefit from galantamine measured by the CIBIC-plus compared with placebo at 13–16 weeks. When the new studies' data were pooled with existing evidence, the overall pooled estimates of the CIBIC-plus at 26 weeks showed a statistically significant benefit from galantamine compared with placebo (a mean change from baseline versus placebo of 0.196 [p < 0.001] at 26 weeks). According to the manufacturer of galantamine, established randomised controlled trial data showed that in four out of five placebo-controlled trials in people with mild to moderate Alzheimer's disease, statistically significant benefits of galantamine were seen with CIBIC-plus. This statistically significant benefit was reflected in the

pooled data (including the subgroup of patients with additional cerebrovascular disease from another trial).

4.1.19 The Assessment Group noted that none of the new randomised controlled trials included in the assessment report provided any additional data on quality of life, time to institutionalisation or mortality with galantamine.

4.1.20 According to the Assessment Group, overall for galantamine in two new studies, there was a high percentage of any adverse event in both studies in treatment and control groups (any adverse events: treatment = 79–84%, placebo = 62–70%). The manufacturer of galantamine did not present any new data on toxicity.

4.1.21 The Assessment Group included a systematic review, including a meta-analysis, that concluded that the AChE inhibitors provided benefits in terms of cognitive function and activities of daily living, and galantamine improved psychological symptoms in mild to moderate dementia.

Rivastigmine versus placebo

4.1.22 The Assessment Group included three new randomised placebo-controlled comparisons of rivastigmine. No data were submitted by the manufacturer of rivastigmine.

4.1.23 Three new studies for rivastigmine were identified by the Assessment Group that measured cognition using ADAS-cog and/or MMSE and showed significant benefit (patch and capsule were not differentiated). When the results of these were added to the randomised controlled trials in NICE technology appraisal guidance 111, it demonstrated a statistically significant improvement in cognition with rivastigmine compared with placebo at 24–26 weeks (mean changes from baseline versus placebo of 1.022 [$p < 0.001$] using MMSE score and −2.464 [$p < 0.001$] using ADAS-cog score).

4.1.24 Two of the three new studies found by the Assessment Group published since 2004 reported statistically significant functional benefit from rivastigmine compared with placebo. These used the Progressive

Deterioration Scale (PDS) and ADCS-ADL as outcome measures. The overall pooled estimate using the new and previous data for PDS at 24–26 weeks showed a statistically significant benefit of rivastigmine compared with placebo (a mean change from baseline versus placebo of 3.103 [$p < 0.001$] at 24–26 weeks using PDS score). Two new studies were found to add to the pooled multiple outcome measure analysis of functional outcomes at 24–26 weeks, which showed a statistically significant benefit from rivastigmine compared with placebo.

4.1.25 Two new studies were found that measured behavioural outcomes with rivastigmine. One small study found a statistically significant benefit from rivastigmine. The other, much larger, study did not. The Assessment Group stated that the data identified by this review and NICE technology appraisal guidance 111 are sparse and too heterogeneous to permit meaningful quantitative synthesis.

4.1.26 The two new studies in this comparison that reported global outcomes had conflicting results. One found mostly significantly favourable results with the CIBIC-plus and the Global Deterioration Scale (GDS), but the other did not. Data from the new studies were pooled with the existing evidence in a random-effects meta-analysis using the CIBIC-plus and the GDS at 26 weeks. The meta-analysis showed a statistically significant benefit from rivastigmine at 26 weeks (mean changes from baseline versus placebo of 0.420 [$p < 0.001$] using CIBIC-plus score and 0.196 [$p < 0.001$] using GDS score). The pooled multiple outcome measure analysis showed an overall statistically significant benefit for rivastigmine compared with placebo.

4.1.27 The Assessment Group noted that none of the new randomised controlled trials included in the assessment report provided any additional data on quality of life, time to institutionalisation or mortality with rivastigmine.

4.1.28 According to the Assessment Group, for rivastigmine, overall there was a high percentage of any adverse events, ranging from 51% to 91% in the treatment groups, and 46% to 76% in control groups. The main adverse events were gastrointestinal. The 9.5 mg/day transdermal patch produced fewer side effects than the capsule (12 mg/day).

4.1.29 The Assessment Group included a Cochrane review that concluded that high doses of rivastigmine offered statistically significant benefits in patients with mild to moderate Alzheimer's disease versus placebo.

Head-to-head and mixed treatment comparison

4.1.30 The Assessment Group identified four head-to-head randomised controlled trials (two comparing all three AChE inhibitors, one comparing donepezil with rivastigmine and one comparing donepezil with galantamine) but considered only one of the studies to be of sufficiently high quality to inform this review. The included study (which compared donepezil with rivastigmine) noted that over 2 years there was no statistically significant difference between rivastigmine and donepezil for cognitive outcomes (MMSE and SIB). Patients taking rivastigmine had significantly improved outcomes than those taking donepezil in the primary analysis of functional outcomes ($p = 0.007–0.047$). No significant difference was seen between donepezil and rivastigmine for behavioural outcomes (NPI). The study showed that patients taking rivastigmine did significantly better than those taking donepezil in terms of global outcomes (GDS). However, the manufacturer of donepezil stated that this study did not meet its primary endpoint and showed higher discontinuations and higher rates of some adverse events for rivastigmine compared with donepezil. None of the newly identified, head-to-head, randomised studies investigated quality of life with the technologies under assessment, and no such data were identified in NICE technology appraisal guidance 111. The most common adverse effects reported in the head-to-head studies of the AChE inhibitors were nausea, diarrhoea, vomiting and headache.

4.1.31 If data were sufficient, the Assessment Group pooled information on all technologies and their comparators simultaneously in a mixed treatment comparison, using Bayesian Markov Chain Monte-Carlo sampling, which showed the probability of each treatment being the most clinically effective. The results of the mixed treatment comparison varied depending on the symptom assessed, the instrument used and follow-up time. The Assessment Group included a systematic review, including a meta-analysis, that concluded that the AChE inhibitors provided benefits in terms of cognitive function and activities of daily living, and

galantamine improved psychological symptoms in mild to moderate dementia. Another concluded that for the AChE inhibitors and memantine there was a small effect size in mild to moderate Alzheimer's disease.

Moderate to severe Alzheimer's disease

Memantine monotherapy versus placebo

4.1.32 The Assessment Group found one new randomised controlled trial for memantine monotherapy versus placebo. The manufacturer of memantine submitted estimates of clinical effectiveness for the general population with moderate to severe Alzheimer's disease and a subgroup of patients with agitation, aggression and/or psychotic symptoms. The manufacturer submitted a meta-analysis that had used individual patient data from six 6-month randomised controlled trials. The first three trials were in moderately severe to severe disease and the other three were in mild to moderate disease. The Assessment Group had excluded trials in which at least 20% of the study participants had mild disease because this was outside the marketing authorisation for memantine. The manufacturer included data from patients with moderate disease only in these trials using the individual patient data. In addition, the manufacturer included trials of monotherapy and combination therapy in the pooled results presented in this section whereas the Assessment Group analysed each separately. Evidence from prospective longitudinal and observational studies was also presented.

4.1.33 One new randomised controlled trial of memantine monotherapy included by the Assessment Group showed a statistically significant benefit in a cognitive measure using SIB with memantine compared with placebo. When data from this trial were added to those of NICE technology appraisal guidance 111, a statistically significant benefit was reported at 12 weeks, but this was not maintained at 24–48 weeks (mean changes from baseline versus placebo of 4.147 [p = 0.025] and 3.254 [p = 0.245] at 12 and 24–28 weeks using SIB score). Studies included in the manufacturer's meta-analysis for memantine reported a statistically significant benefit in ADAS-cog and SIB compared with placebo at the end of study and at 24 weeks (standardised mean difference = −0.26, p < 0.0001).

4.1.34 The results from the new study included by the Assessment Group showed no significant benefit in functional outcome measured by ADCS-ADL for memantine monotherapy compared with placebo at 12 weeks or when measured with the Functional Assessment Staging (FAST) instrument. The data were synthesised with the existing evidence in random-effects meta-analysis. Two studies provided data for functional effect as measured by ADCS-ADL19 version. The results were not statistically significant at 12 weeks and were only just significant at 24–28 weeks (mean changes from baseline versus placebo of 0.877 [p = 0.075] and 1.408 [p = 0.044] at 12 and 2428 weeks respectively using ADCS-ADL score and −0.341 [p = 0.002] at 24–28 weeks respectively using FAST score). The manufacturer's meta-analysis for memantine in moderate to severe disease showed a statistically significant difference compared with placebo on the ADCS-ADL19 and ADCS-ADL23 (standardised mean difference = −0.18, p < 0.0007).

4.1.35 The study for memantine monotherapy that was published after 2004 and included by the Assessment Group measured behavioural outcomes using NPI and the Behavioural Rating Scale for Geriatric Patients (BGP). Neither measure showed a statistically significant benefit of memantine. The data were pooled with the existing data at 24–28 weeks, which did not show a statistically significant gain from memantine compared with placebo (a mean change from baseline versus placebo of −1.608 (p = 0.314) at 24–28 weeks using NPI score). The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant (p = 0.03) benefit in terms of NPI and NPI-Nursing Home version (standardised mean difference = −0.12, p = 0.03).

4.1.36 According to the Assessment Group, one new study for memantine monotherapy measured global outcomes with the CIBIC-plus but the differences found were not statistically significant. When new data were pooled with the existing studies, the overall pooled estimate showed a statistically significant beneficial effect from memantine compared with placebo (a mean change from baseline versus placebo of −0.300 [p < 0.001] at 24–28 weeks using CIBIC-plus score). Studies included by the manufacturer in the meta-analysis for memantine used CIBIC-plus or the Alzheimer's Disease Cooperative Study – Clinical Global Impression

of Change (ADCS-CGIC). The standardised mean difference in the manufacturer's meta-analysis for memantine in moderate to severe disease for global outcomes (CIBIC-plus) compared with placebo was statistically significant (standardised mean difference = −0.22, $p < 0.0001$).

4.1.37 The Assessment Group noted that none of the new randomised studies included in the assessment report provided any additional data on quality of life, time to institutionalisation or mortality with memantine.

4.1.38 The manufacturer of memantine included an analysis of a subgroup of patients with moderate to severe Alzheimer's disease with agitation, aggression and/or psychotic symptoms to show that memantine offers enhanced benefits in this subgroup in terms of cognition and function. The manufacturer also included an indirect comparison with risperidone, which was not a comparator in the scope and therefore outside the scope of this review. This analysis was not included by the Assessment Group because no subgroup analyses or individual patient data had been published. The MAG-D study was ongoing at the time of writing the assessment report, so was not included by the Assessment Group. In addition, the manufacturer of memantine submitted data from prospective longitudinal and observational studies to support the view that cognitive and functional benefits of memantine are maintained over years, that memantine delays time to institutionalisation, reduces the need for antipsychotic use and that discontinuation of memantine is associated with an increased use of antipsychotics compared with continuous memantine treatment.

4.1.39 According to the Assessment Group, the proportion of any adverse events for memantine in the new study was similar in treatment and control groups (treatment = 74%, control = 73%). The main adverse events in the memantine group were agitation and hypertension, and agitation and falls in the control group. This did not change assumptions about the safety of memantine from technology appraisal guidance 111. The manufacturer highlighted a published meta-analysis of safety data from clinical trials which also showed the most common adverse events with memantine to be agitation and falls. However, it noted that both have a numerically lower incidence than placebo.

Memantine combination therapy

4.1.40 The Assessment Group found one new study of memantine in combination with any of the AChE inhibitors. It assessed the clinical effectiveness of memantine combination therapy separately from monotherapy. This was different from the approach taken in NICE technology appraisal guidance 111 and by the manufacturer of memantine. The Assessment Group found one new trial that compared memantine plus a stable dose AChE inhibitor with an AChE inhibitor plus placebo. This trial did not show any benefit from combining memantine with an AChE inhibitor on cognitive, functional, behavioural or global outcomes. A trial that compared memantine plus donepezil with donepezil plus placebo was included in NICE technology appraisal guidance 111. Pooling the new trial with the previous trial of memantine in combination with an AChE inhibitor did not show any additional benefit from combination therapy. The manufacturer of memantine commented that its submitted meta-analysis of six trials showed memantine to be significantly superior to placebo on most outcomes, as adjunct and monotherapy. It also stated that interaction between treatment effect and presence of background treatment was found not to be significant.

4.1.41 The manufacturer of memantine referred to safety reports since 2002, two safety reviews and a meta-analysis. It concluded that memantine was well tolerated when used as monotherapy or as combination therapy.

Summary

4.1.42 The Assessment Group identified 17 new randomised controlled trials and four systematic reviews of randomised controlled trials. According to the Assessment Group, there was an increase in the amount and precision of available evidence for the clinical effectiveness of the AChE inhibitors and memantine. For the AChE inhibitors, the new studies supported and strengthened the previous evidence of benefit in terms of cognitive outcomes, but results for other outcomes were mixed. For memantine monotherapy, the new evidence did not support evidence of statistically significant benefit compared with placebo for any outcome, but the pooled evidence with previous evidence from before 2004

showed improvement in cognition at 12 weeks and in function at 24–28 weeks.

4.1.43 The Assessment Group concluded that the evidence for monotherapy in the three manufacturer's submissions was broadly consistent with its own, but highlighted that there were differences between the studies included by the manufacturers and its own review. In addition, the Assessment Group analysed monotherapy and combination therapy separately, whereas the manufacturer of memantine combined the two in its submitted meta-analysis.

4.1.44 The Assessment Group considered the quality of the new placebo-controlled studies published since 2004 to be 'disappointing'. Issues included the inappropriate use of last observation carried forward and observed cases analysis instead of intention-to-treat analysis, inadequate reporting of randomisation and allocation, and the small size of studies for donepezil in particular. According to the Assessment Group, the robustness of the new evidence provided by the head-to-head studies was limited by the poor quality of all but one of the studies. Important gaps in the evidence remain.

4.2 Cost effectiveness

4.2.1 The Assessment Group conducted a systematic review of published economic evaluations since 2004. The Assessment Group, the manufacturer of donepezil (Eisai/Pfizer) and the manufacturer of memantine (Lundbeck) submitted new economic models. The Assessment Group's model included all technologies. Because of differences in the marketing authorisations, the base-case cost effectiveness of the AChE inhibitors and memantine were modelled separately in mild to moderate and moderate to severe disease respectively. No new economic models were submitted by the manufacturers of galantamine and rivastigmine. The manufacturer of galantamine highlighted issues with the previous model from NICE technology appraisal guidance 111.

Mild to moderate Alzheimer's disease

Donepezil

4.2.2 The Assessment Group conducted a systematic review of published economic evaluations since 2004. It identified eight studies of cost effectiveness specifically for donepezil and one that reported on the cost effectiveness of both donepezil and rivastigmine. According to the Assessment Group, these publications generally supported the cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease.

Manufacturer's model for donepezil

4.2.3 The manufacturer of donepezil submitted an economic model that compared the cost effectiveness of donepezil with best supportive care in people with mild to moderate Alzheimer's disease using a discrete event simulation approach over a lifetime. The baseline characteristics of the model population (including age, sex, race, measures of cognition [MMSE], function [ADL and instrumental ADL (IADL)], behaviour [NPI] and concomitant treatments) were based on 221 people with mild disease and 605 people with moderate disease from a pool of three randomised controlled trials. The model used a weighted sampling approach to sample 1000 individuals from the pooled trial populations, and these individuals were then replicated in the model and allocated to donepezil or no AChE inhibitor treatment. Disease progression and treatment effect were measured using cognition (MMSE), activities of daily living (ADL and IADL) and behaviour (NPI). Regression equations were formulated based on data from a US registry (the CERAD study) and seven donepezil clinical trials spanning mild to severe Alzheimer's disease and including data from two open-label extensions of the studies. The updated MMSE score was then used to predict the change in ADL, IADL and NPI. The proportion of people institutionalised depended on severity of Alzheimer's disease.

4.2.4 The effectiveness of donepezil in the manufacturer's model was derived from a meta-analysis of six pooled randomised controlled trials and assumed the same treatment effect for both mild and moderate

Alzheimer's disease. The model updated patient characteristics every 3 months. Discontinuation data were taken from 88 patients. Patient utilities were based on a Swedish study using the EQ-5D and carer proxy responses. Carer utilities were estimated using SF-36 scores and the Brazier algorithm from three clinical trials. Carer utility accounted for approximately 10% of the incremental quality-adjusted life years (QALYs) but did not include the impact on carer utility of patients entering an institution. NHS and personal social services costs were included along with costs to the individual and their family. NHS reference costs, list drug prices (including a price reduction effective after the November 2009 Pharmaceutical Price Regulation Scheme, which was later published in the BNF60) and a report by Dementia UK (2007) were used for cost estimates, which were inflated to current prices. Costs included a consultation visit that took place every 6 months during treatment. Cost and benefits were discounted at 3.5%.

4.2.5 The manufacturer's base-case results estimated that donepezil dominated best supportive care because it was less costly and more effective in people with mild, moderate and mild to moderate Alzheimer's disease. The manufacturer reported per patient QALY gains of 0.133 and 0.098 and estimated total per patient cost saving of £3379 and £1889 for groups with mild and moderate disease respectively. When the overall mild to moderate disease population was considered, total cost savings amounted to £2354 and people gained an average of 0.109 QALYs including patient utility alone, and 0.121 including patient and carer utilities. The manufacturer of donepezil estimated a delay to institutionalisation of 2 months.

4.2.6 All but one of the one-way sensitivity analyses conducted by the manufacturer of donepezil in the mild and moderate disease populations (including varying the time horizon, discount rate, MMSE progression, treatment effect, discontinuation, treatment duration, costs of care, costs of nursing home care, patient and carer QALY effect, costs of physician visits, and the 30–50% reduced price of donepezil after loss of patent protection in 2012) resulted in donepezil being dominant. The exception was when nursing home costs were reduced by 50%, which changed the incremental difference in costs from a cost saving of £3379 in the base case to an increased cost of £275, which gave an incremental

cost-effectiveness ratio (ICER) of £1866 per QALY gained for mild Alzheimer's disease. When nursing costs were reduced in the moderate disease population, the costs were increased from a cost saving of £1889 in the base case to a cost of £1370, giving an ICER of £7093 per QALY gained. The probabilistic sensitivity analysis reported a 74% and 70% probability of donepezil being cost effective at a threshold of £20,000 per QALY gained in the mild and moderate disease populations respectively (and a 78% and 74% probability respectively at a threshold of £30,000 per QALY).

4.2.7 Issues raised by the Assessment Group included:

- the generalisability of the CERAD (US-based) study
- potential double counting of improvement in MMSE score in the regression equations for NPI, ADL and IADL
- the data for the probability of needing institutionalised care being based on a nursing home population
- uncertainty about the quality of inputs, including the link that was made between MMSE and institutionalisation and overestimation of treatment effect
- excluding a possible increase in carer utility after institutionalisation
- including non-NHS/personal social services costs
- including cost and utility inputs based on a cohort approach
- uncertainties about the probabilistic sensitivity analysis.

4.2.8 The Assessment Group made several changes to the manufacturer's model, which included corrected MMSE scaling, hazard calculations and life expectancy. These amendments had little impact on the manufacturer's deterministic and probabilistic ICERs, which continued to show that donepezil dominated best supportive care in mild and moderate Alzheimer's disease. The Assessment Group also ran its own assumptions through the model and this also did not change the outcome of dominance.

4.2.9 In response to comments in the assessment report, the representative of

the manufacturer of donepezil stated that the improvement in MMSE score had not been double counted in its model. The manufacturer also clarified that a survival effect had not been included.

Rivastigmine and galantamine

4.2.10 The Assessment Group conducted a systematic review of published economic evaluations since 2004. It identified one study of cost effectiveness specifically for rivastigmine, two for galantamine, and one that reported on the cost effectiveness of both donepezil and rivastigmine. According to the Assessment Group, these publications generally supported the cost effectiveness of the AChE inhibitors in mild to moderate Alzheimer's disease. Most of the publications applied the existing model of Alzheimer's disease (from NICE technology appraisal guidance 111) to new settings.

4.2.11 The manufacturers of galantamine and rivastigmine did not submit new economic models. The manufacturer of galantamine highlighted issues with the previous model from NICE technology appraisal guidance 111 including:

- the need to include long-term efficacy data
- recognition of the full impact of decline in untreated patients with mild disease
- overestimation of mortality
- the need for current cost data
- recognition of 'no change' on global efficacy after 6 months or longer
- consideration of costs to the individual, carer time and costs
- exploration of responder analyses.

Assessment Group's model - mild to moderate Alzheimer's disease

4.2.12 The Assessment Group modelled the cost effectiveness of the AChE inhibitors and memantine separately because of the differences in the marketing authorisations. The base-case model for the AChE inhibitors

followed a cohort of 1000 individuals with mild to moderate (MMSE 26–10) Alzheimer's disease for which the comparators were donepezil, rivastigmine (patch and capsule), galantamine and best supportive care. The Assessment Group used a prevalent cohort approach. Differentiation of treatment effect according to severity of disease (that is, mild or moderate) was not included in the base-case model. Populations with mild and moderate disease were assessed individually in the sensitivity analyses.

4.2.13 The Assessment Group's base case for mild to moderate disease evaluated the cost effectiveness of the AChE inhibitors over a lifetime (20-year) time horizon. Memantine was not included in the base case for mild to moderate disease. The Assessment Group constructed a Markov model that estimated the time to institutionalisation, which was defined as 'living in a residential home or a nursing home (not short respite care) or in a hospital on a long-term or permanent basis'. The model included three health states: pre-institutionalisation, institutionalisation and death. Depending on the severity of Alzheimer's disease at the beginning of the model, people could enter the model in the pre-institutionalised or institutionalised health state. Institutionalisation was equivalent to severe Alzheimer's disease (MMSE < 10) at which point treatment with an AChE inhibitor stopped in line with the marketing authorisations. Individual patients' data were used to estimate the proportion of the total cohort in each state at the end of each monthly cycle. An exponential survival regression model was fitted with time to end of pre-institutionalisation (including early death) as the response variable and MMSE, Barthel-ADL and age at start of study as covariates. The model incorporated a gradual increase in costs and gradual reduction in health-related quality of life with time. Cost and benefits were discounted at a rate of 3.5%. A constant rate of 4% discontinuation per monthly cycle for all drugs at all doses was assumed following a review of the included clinical trial evidence. Therefore within 25 months all patients were assumed to have stopped treatment.

4.2.14 Patient characteristics (cognition [MMSE] and function [the Barthel-ADL] with three subgroups defined by age) were based mainly on individual patients' data from a community-based cohort study of people with untreated Alzheimer's disease by Wolstenholme and colleagues in

Oxfordshire (n = 92). People starting in the model had already been diagnosed with Alzheimer's disease for a median of 4.0 years and a mean of 4.9 years. Data from the London and South-East Region Alzheimer's Disease (LASER-AD) study were used to predict the proportion of patients who, at the start of the decision model, were in the institutionalised state (10% for the mild to moderate cohort and 40% for the moderate to severe cohort, based on 5.6% of people with MMSE ≥ 19, 27.1% of people with MMSE 1519 and 59% people with MMSE < 19). In the base-case analysis, it was assumed that treatment delayed time to institutionalisation but not to death. Time to death was predicted by age, cognition (MMSE) and function (ADL) using equations from the Wolstenholme cohort data.

4.2.15 Estimates of treatment effect in the Assessment Group's model (MMSE and ADCS-ADL, in particular) taken from the placebo-controlled randomised controlled trials identified in the systematic review of clinical effectiveness were applied to baseline estimates of best supportive care for time to institutionalisation and death. Estimates of clinical effectiveness were slightly different to those in the clinical effectiveness section of the assessment report in that only randomised controlled trials of licensed doses were considered. Rivastigmine patches were considered separately to capsules. The assessment report noted literature highlighting that patients self-report much higher utilities than those estimated by carers, particularly in people with severe Alzheimer's disease. Therefore, the base-case model included patient utilities based on carer-proxy utility values. Self-reported patient utilities and carer utilities were included in the sensitivity analysis. Carer utility associated with caring for patients with different CDR severities of Alzheimer's disease was mapped onto the MMSE scale. The utility of caring for someone with mild dementia (MMSE 21–26) was 0.87, which was reduced to 0.86 when caring for someone with severe dementia (MMSE of less than 10). The source publication (Jonsson and colleagues) reported only the mean utility values and not the uncertainty in the utility estimates.

4.2.16 The monthly drug costs included in the Assessment Group model, based on the BNF edition 58, were £83 for galantamine, £97 for donepezil, £79 for rivastigmine patches, and £72 for rivastigmine capsules. Additional

resource use in the Assessment Group's model was estimated from the Wolstenholme cohort study. The cost of outpatient visits was assumed to be £26 per month and £158 for a 6-monthly assessment. The overall mean monthly cost of institutionalised care was estimated at £2941 (28% of which was assumed to be self-funded) and the cost of pre-institutionalised care depended on the severity of disease and the time to institutionalisation (for example, 1 year before institutionalisation the mean monthly costs for people with mild to moderate Alzheimer's disease was £1938 per month compared with £2427 per month for people with moderate to severe Alzheimer's disease). No adverse events or carer costs were included in the economic model.

4.2.17 After comments from consultees and commentators on the assessment report, the Assessment Group made changes to the modelling of treatment effect based on the equations predicting time to institutionalisation and overall survival using age, cognition and function, and the resulting ICERs quoted in the assessment report. The Committee considered the revised outputs only.

4.2.18 The Assessment Group presented the revised deterministic ICERs and one-way sensitivity analysis (which included an analysis of the robustness of the ICERs to different structural assumptions) and the probabilistic ICERs (which represent the combined effect of some of the parameter uncertainties in the model) for each of the technologies. The deterministic model estimated that treatment with an AChE inhibitor delays time to institutional care by between 1.4 and 1.7 months. The deterministic base-case analyses and the probabilistic sensitivity analysis indicated that all AChE inhibitors dominated best supportive care. Galantamine was associated with the least costs (£69,592 compared with £70,212 for best supportive care) but donepezil was associated with the greatest QALY gains (1.619 compared with 1.584 with best supportive care). The Assessment Group noted that the differences in the costs and QALYs between the AChE inhibitors were very small (total costs ranged from £69,592 to £69,678 and total QALYs ranged from 1.613 to 1.619). The probabilistic sensitivity analysis results did not indicate a particular AChE inhibitor as having a much greater probability of being cost effective compared with any of the other AChE inhibitors. For example, rivastigmine patches had the highest probability (32%) of

being cost effective at thresholds of £20,000 and £30,000 per QALY gained, whereas donepezil had a probability of 27% of being the most cost-effective treatment option at a threshold of £20,000 and of 28% at a threshold of £30,000 per QALY.

4.2.19 The Assessment Group conducted one-way sensitivity analyses on the sensitivity of the ICERs to different parameters. The most important parameters were whether a treatment effect on survival was assumed and the rate of discontinuation of drug therapy. Assuming that there was a positive effect of treatment on mortality for all treatments of 1.9 to 2.2 months, it was estimated that treatment with rivastigmine patches provided an additional 0.077 QALYs per patient compared with best supportive care, with additional costs of £2840, leading to an ICER of £37,100 per QALY gained. This was in contrast to rivastigmine patches dominating best supportive care in the base case. In the incremental analysis, when including survival effect as a one-way sensitivity analysis, treatment with galantamine or donepezil provided additional QALYs and additional costs compared with rivastigmine patches. This led to ICERs of £41,800 per QALY gained for galantamine compared with rivastigmine patches, and £51,800 per QALY gained for donepezil compared with galantamine. The Assessment Group explained that this increase in the ICER was expected because when no survival effect was assumed (as per the base case), the delay in time to institutionalisation with treatment resulted in substantial savings in the costs that would have been incurred as a consequence of living in an institution. Assuming that there was also a survival benefit with treatment meant that the costs incurred from living in an institution would be delayed, but not saved. Therefore the incremental difference in costs would be higher and the ICER would increase. Lowering the estimate of the discontinuation rate below 4% resulted in greater treatment and monitoring costs and this led to a negative net benefit for the AChE inhibitors. Higher estimates led to fewer costs and greater net treatment benefit.

4.2.20 The manufacturer of donepezil and the Assessment Group both reported that donepezil treatment dominated best supportive care for both the mild and moderate populations. However, the manufacturer reported per patient QALY gains of 0.133 and estimated total per patient cost savings of £3379 for people with mild disease compared with 0.034 QALY gains

and a saving of £551 in the Assessment Group's model. The manufacturer reported per patient QALY gains of 0.098 and estimated total per patient cost savings of £1889 for people with moderate disease compared with 0.035 QALY gains and a saving of £621 in the Assessment Group's model.

4.2.21 Differences between the results of Assessment Group and manufacturer's models may be accounted for by the following:

- differences between the models in terms of estimated overall survival (4.6 undiscounted life years for the moderate cohort for the manufacturer compared with 3.6 years for the Assessment Group)
- percent of remaining lifetime spent living in the community (40% in the manufacturer model compared with 67% in the Assessment Group's model for the moderate cohort)
- assumptions of treatment effect, calculation of pre-institutionalisation cost (MMSE in the donepezil model compared with time to institutionalisation in the Assessment Group's model)
- differences in the cost of institutional care (£2801 per month in the donepezil model compared with £2117 in the Assessment Group's model)
- inclusion of carer utility
- inclusion of non-NHS/personal social services costs (that is, costs to the individual of institutional care).

4.2.22 The Assessment Group also considered the differences in its model compared with the model from NICE technology appraisal guidance 111 (the SHTAC model). The key differences in the Assessment Group's model were that:

- the sources used to model disease progression were different
- updated estimates of costs and effectiveness were used
- costs and utilities were varied according to time before institutionalisation

- discontinuation of treatment was accounted for.

  The SHTAC model used a risk equation to predict time to needing full-time care. This was based on US data (n = 236), in which a number of different domains (ADAS-cog, psychiatric symptoms, extrapyramidal symptoms, age of onset and duration of illness) affected the time to institutionalisation. The Assessment Group's model, in contrast, was based on UK data (n = 92) and assumed that age and MMSE score predicted institutionalisation. The results of the models differed in the time spent in the institutionalised or full-time care states, which consequently affected costs. A longer estimated survival in the SHTAC model compared with the Assessment Group's model (6.5 compared with 3.8 years) led to higher total costs and total QALYs in the SHTAC model. The Assessment Group assumed less of a treatment effect for an AChE inhibitor, which translated to a slightly shorter delay to full-time care or institutionalisation (approximately 2 months in the SHTAC model compared with 1.4 to 1.7 months in the Assessment Group's model). The costs in the pre-institutional state in the Assessment Group's model were varied according to time, which led to lower average costs in the pre-institutional state in the Assessment Group's model. The difference in incremental costs in the Assessment Group model compared with the SHTAC model was a key factor in the different estimates of costs effectiveness (for example, an ICER of over £30,000 per QALY gained in the SHTAC model for donepezil, compared with donepezil dominating best supportive care in the Assessment Group's model). Including discontinuation of treatment in the Assessment Group's model led to fewer costs and greater net benefit associated with the AChE inhibitors, and so when discontinuation of treatment was included in the SHTAC model, this reduced the estimated ICER.

4.2.23 The Assessment Group noted some limitations of its model. These were that:

- it assumed a treatment benefit in cognition and function but not in behavioural and psychological symptoms
- the expression of treatment effectiveness was mainly based on delay in time to institutionalisation
- changes in cost and utility before institutionalisation were assumed to be delayed by the same amount of time as institutionalisation

- the generalisability of the Wolstenholme cohort to the UK population was uncertain
- full treatment effect at 6 months was assumed.

The Assessment Group presented the deterministic ICER for each treatment to provide a comparison with best supportive care so that the data were comparable with those presented in NICE technology appraisal guidance 111.

Moderate to severe Alzheimer's disease

Memantine

4.2.24 The Assessment Group's systematic review of literature published since 2004 identified six new cost-effectiveness studies for memantine. According to the Assessment Group, these publications generally supported the cost effectiveness of memantine for the treatment of Alzheimer's disease.

Manufacturer's model for memantine

4.2.25 The manufacturer submitted a Markov cohort model of the cost effectiveness of memantine compared with best supportive care over a 5-year time horizon in people with moderate to severe Alzheimer's disease and a subgroup of people with aggression, agitation and/or psychotic symptoms at baseline based on the NPI scale (at least one domain among agitation/aggression, delusion and hallucination with a score $\geq$ 3). The model included three states: pre-full-time care; full-time care; and death. Full-time care was defined as either dependent or institutionalised. Transition probabilities, including the baseline probability (on no treatment) of moving from pre-full-time care to full-time care and the probability of death were estimated using data from the LASER-AD UK epidemiological study. Predictors of the length of time to patients entering full-time care included measures of cognition (ADAS-Cog), function (ADCS-ADL), behaviour (NPI) and time in months. The clinical effectiveness of memantine, for which no additional benefit was assumed beyond 6 months, was based on a meta-analysis of six clinical trials of patients with moderate to severe Alzheimer's disease receiving

memantine monotherapy or memantine adjunct treatment while on a stable dose of AChE inhibitors. Weighted mean differences were used as predictors in the risk equation estimating monthly probability of entering full-time care to incorporate treatment effect. NHS and personal social services costs were included. Resource use data were taken from the LASER-AD study and the Personal Social Services Research Unit (PSSRU). MIMS March 2010 was used for costs, which were discounted at 3.5%. Indirect costs and quality-of-life effects on relatives and carers were not included. Utility estimates were derived from the LASER-AD study, which involved mapping of three instruments (HSQ-12, Ferm's D test and QoL-AD) onto the EQ-5D. The manufacturer ran the model probabilistically.

4.2.26 The manufacturer found that memantine dominated best supportive care (that is, no pharmacological treatment) because additional QALYs were gained (0.031) at a cost saving of £1711. Memantine treatment was associated with a delay to full-time care of 6 weeks. Additional treatment benefits were reported in the subgroup of patients with aggression, agitation and/or psychotic symptoms in whom the delay to full-time care was prolonged by up to 11 weeks with incremental QALY gains of 0.069 and a cost saving of £4971.

4.2.27 The manufacturer conducted sensitivity analyses. These explored the effect of different treatment effects, discount rates, costs of pre-full-time care, costs of full-time care and alternative sets of utilities on the cost-effectiveness estimates. The results all continued to show that memantine dominated best supportive care for the overall population and subgroups.

4.2.28 The Assessment Group highlighted several issues with the manufacturer of memantine's model. Although the new subgroup was defined differently and based on clinical expertise, the Assessment Group noted that a behavioural subgroup had not previously been accepted by the Appraisal Committee for NICE technology appraisal guidance 111. The manufacturer did not include an AChE inhibitor as a comparator for the population with moderate disease as specified in the scope. There was uncertainty about the risk equation because of lack of clarity over generalisability of the LASER-AD study (many participants in this study

had been or were still receiving treatment with AChE inhibitors). The Assessment Group also noted a lack of clarity about the categorisation of 'dependence', inclusion of data from patients with mild disease, poor reporting of statistical analyses and lack of validation from an external source. The manufacturer responded to these criticisms, providing supplementary information in its comments on the assessment report. In addition, because the trials used observed cases with last observation carried forward in the analysis instead of an intention-to-treat analysis, the Assessment Group was concerned that the clinical-effectiveness estimates may have been biased. The manufacturer responded to these comments to confirm that all analyses were performed with an intention-to-treat population using the observed cases approach, with a 'last observation carried forward' analysis to confirm results. There was also uncertainty about the methods used to map one outcome measure to another (mapping one health-related quality-of-life measure onto another, mapping SIB onto the ADAS-cog and rescaling one version of ADCS-ADL to another), pooling data for combination therapy and monotherapy, and using NPI rather than NPI hallucinations as a predictor of time to full-time care. There was also a lack of clarity over the sources of data, inclusion of costs to individuals and retrospective collection of resource data in the LASER-AD study. Benefits to carers were not included in the model, and mapping of health-related quality-of-life data to EQ-5D was poorly described. The Assessment Group queried whether the manufacturer's estimates of at least 90% for the probability of memantine being cost effective at £20,000 and £30,000 thresholds were plausible given the uncertainties about the clinical benefit of memantine.

Assessment Group's model – moderate to severe Alzheimer's disease

4.2.29 The cost effectiveness of the AChE inhibitors and memantine were modelled separately by the Assessment Group because of the differences in the marketing authorisations. Memantine was not included in the SHTAC model in NICE technology appraisal guidance 111. The base-case model for memantine followed a cohort of 1000 individuals with moderate to severe (MMSE 200) Alzheimer's disease, for which the comparator was best supportive care. Populations with moderate and severe disease were assessed individually in the sensitivity analyses. The Assessment Group's model is described in sections 4.2.12 to 4.2.16.

Different assumptions used in the moderate to severe model were that a higher proportion of people started in institutional care (40% compared with 10% in the mild to moderate model) and treatment with memantine was continued after people entered institutional care (whereas treatment with AChE inhibitors was discontinued when people entered institutional care in the mild to moderate model). The cost of monthly memantine was £71.

4.2.30 The deterministic Assessment Group's model showed that treatment with memantine delayed time to institutional care by about 0.8 months compared with best supportive care. The ICERs were £32,100 per QALY gained (a gain of 0.013 QALYs over a patient's lifetime when treated with memantine compared with best supportive care and the extra cost was £405).

4.2.31 The Assessment Group's probabilistic sensitivity analysis of the cost effectiveness of memantine in the population with moderate to severe Alzheimer's disease estimated a probability of memantine being more cost effective than best supportive care of less than 38% at a threshold of £30,000 per QALY gained and 28% at £20,000 per QALY gained. The mean ICER from the probabilistic sensitivity analysis for memantine compared with best supportive care was £36,900 per QALY gained.

4.2.32 The Assessment Group conducted one-way sensitivity analyses to assess the sensitivity of the ICER to different parameters. When a positive treatment effect on survival was assumed, the ICER of memantine compared with best supportive care increased to £65,619 per QALY gained.

4.2.33 The cost-effectiveness model submitted by the manufacturer of memantine reported that treatment with memantine dominated best supportive care. The Assessment Group's model, however, estimated an ICER of £32,100 per QALY gained. One of the main differences between the manufacturer's model and the Assessment Group's model was that treatment was assumed to continue in institutionalisation by the Assessment Group but not the manufacturer. The estimated overall survival was similar in the two models (3.7 years in the manufacturer's model and 3.5 years in the Assessment Group's model). Another key

difference between the models was that the manufacturer's model assumed a greater treatment effect with memantine, which translated to a delay to entering full-time care of 1 month compared with a delay of 0.8 months estimated by the Assessment Group's model. Higher costs were attributed to the full-time care state in the manufacturer's model (£3267 compared with £2117 in the Assessment Group's model). The manufacturer's model also assumed a higher cost of, and a longer time in, pre-institutional care with treatment (1.73 years in the manufacturer's model compared with 1.5 years in the Assessment Group's model).

4.2.34 The Assessment Group ran the manufacturer of memantine's model using its own assumptions. This had a negligible impact on the outputs.

Assessment Group's model – subgroups of mild, moderate and severe Alzheimer's disease for all treatments

4.2.35 The Assessment Group conducted analyses of the individual mild, moderate and severe populations for the AChE inhibitors, AChE inhibitors and memantine, and memantine respectively (all including best supportive care). Each technology was compared with the next cheapest, non-dominated technology and the ICERs were rounded to the nearest £100. The Assessment Group highlighted that caution should be taken when assessing these results because effectiveness estimates were derived from trials that included populations with varying disease severity. In the subgroup analyses for mild or moderate Alzheimer's disease, all treatments still dominated best supportive care. Memantine had an ICER of £26,500 per QALY gained in severe disease.

Other key issues

4.2.36 NICE technology appraisal guidance 111 acknowledged the issues in using the MMSE instrument alone as a measure of severity in particular groups. This included people with learning or other disabilities, linguistic or other communication difficulties, or if it is not possible to use the MMSE in a language in which the patient is sufficiently fluent.

4.2.37 Clinical specialists, patient experts and primary care trust commissioners highlighted the need for a wide range of services for people with

Alzheimer's disease, and the fact that drugs are just one aspect of this range of care.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine having considered evidence on the nature of Alzheimer's disease and the value placed on the benefits of donepezil, galantamine, rivastigmine and memantine by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.3.2 The Committee was aware that there is currently no cure for Alzheimer's disease and that the AChE inhibitors and memantine treat the symptoms of Alzheimer's disease but do not slow the progression of the disease. The Committee was also aware that access to general support services and care for people with Alzheimer's disease is variable and that the availability of pharmacological treatment was relevant to appropriate wider management and support. The Committee considered the current management of Alzheimer's disease under the recommendations of NICE technology appraisal guidance 111, which recommends AChE inhibitors for the treatment of moderate Alzheimer's disease. The Committee was aware of both the importance of early diagnosis and of carers' and clinical views of the advantages of early use of AChE inhibitors in the treatment of Alzheimer's disease. The Committee heard from clinical specialists that there is variation in clinical practice and that AChE inhibitors are also used to treat some patients with an MMSE score of above 20. The clinical specialists also noted that memantine is used in clinical practice. The Committee heard from clinical specialists that antipsychotics are used in clinical practice for people with Alzheimer's disease who have severe behavioural symptoms, but that their use was generally discouraged in people with milder symptoms because of the emerging evidence on increased risk of serious adverse events when used in older people.

4.3.3 The Committee heard from clinical specialists that the MMSE scale was originally developed as a screening tool to aid the diagnosis of

Alzheimer's disease. It also heard that NICE technology appraisal guidance 111 had defined the eligibility of people for treatment with AChE inhibitors and when these drugs should be stopped according to MMSE scores (that is, the degree of loss in patient cognition), among other criteria. The Committee noted, as did the Appraisal Committee for NICE technology appraisal guidance 111, that because the MMSE scale is less sensitive to changes in cognition for people at the extreme ends of the scale, clinical judgement is necessary (rather than a rigid adherence to the MMSE alone) to assess the severity of Alzheimer's disease and the suitability of AChE inhibitors on an individual patient basis. In addition, the clinical specialists indicated that a global assessment of the effects of Alzheimer's disease was also important. The Committee was aware of the difficulties of using the MMSE when assessing people with learning difficulties or communication difficulties, or if the person is not fluent in the language of the measurement tool. The Committee also heard from clinical specialists that the use of the MMSE scale alone may not be sensitive enough to assess the severity of Alzheimer's disease in people with a high level of education. The Committee thus recognised the difficulties of using MMSE score alone to assess the severity of Alzheimer's disease and the response to AChE inhibitors. The Committee agreed that cognitive scales alone such as the MMSE are not always appropriate for assessing the severity of dementia. The Committee concluded that if cognitive scales are not appropriate for assessing the need for treatment, or whether to continue treatment, then clinicians should use another appropriate method of assessment.

Clinical effectiveness

Clinical effectiveness donepezil, rivastigmine and galantamine

4.3.4 The Committee considered the available evidence on the clinical effectiveness of the AChE inhibitors submitted by the Assessment Group, consultees and commentators. It considered the new evidence available since NICE technology appraisal guidance 111 was published and the impact of the new evidence when combined with the data from NICE technology appraisal guidance 111. The Committee stated that a small amount of new evidence about the clinical effectiveness of the AChE inhibitors from randomised controlled trials had been published since

2004. The Committee recognised the heterogeneity of outcome measures in trials and was aware of the limitations of some of the instruments used in the clinical trials, including cognitive and behavioural scales.

4.3.5 The Committee considered the results from the new placebo-controlled randomised clinical trials, which continued to show the small but definite clinical benefit of the AChE inhibitors in mild and moderate Alzheimer's disease compared with best supportive care. The Committee noted that the evidence was almost exclusively based on 6-month long randomised controlled trials because few of these trials had follow-up of over 6 months. The Committee heard from clinical specialists and patient experts that benefits of treatment appeared to last for 2 to 3 years in some patients in open-label studies. The Committee concluded that the new evidence provided additional support to the conclusions from 2004 that each of the AChE inhibitors offers benefits over best supportive care for cognitive, functional and global outcomes, and may offer some benefit in behavioural outcomes, although the nature and extent of behavioural benefits are uncertain owing to mixed results from the available evidence.

4.3.6 The Committee considered whether there was evidence that one of the AChE inhibitors was more clinically effective than any other. The Committee noted that only one good-quality head-to-head randomised controlled trial comparing donepezil and rivastigmine had been published since 2004 and that this did not change the conclusions made in NICE technology appraisal guidance 111. The Committee concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of clinical effectiveness.

4.3.7 The Committee considered whether there was evidence that AChE inhibitors demonstrated benefits in terms of patient and carer health-related quality of life. The Committee noted that quality of life was not assessed in the majority of randomised controlled trials and that there was no evidence from randomised controlled trials that demonstrated any impact. The Committee considered evidence from patient experts that benefits to people with Alzheimer's disease and their carers were not necessarily those picked up by instruments measuring cognition,

function, behaviour or global outcomes. In their experience, relevant benefits included maintaining mood, being able to cope and interact with others, and functional activities that might not be scored on currently used scales, such as being able to pick up the phone or switch on the television. In particular, maintaining aspects of personal identity, such as a naturally methodical person being able to put things in order, was considered important. The Committee concluded that although there was no evidence available on health-related quality of life from a systematic review of randomised controlled clinical trials, there was some anecdotal evidence from clinical practice of benefits to patients and carers from using AChE inhibitors.

4.3.8 The Committee discussed whether there was evidence of a survival benefit associated with the AChE inhibitors. The Committee was aware that these are symptom-treating rather than disease-modifying treatments. In the absence of evidence from randomised controlled trials, the Committee considered the opinion of clinical specialists, who were not aware of a survival effect associated with the AChE inhibitors. The Committee acknowledged that few deaths occurred during randomised controlled trials, which have generally been short with limited follow-up, and that subsequently mortality data were difficult to obtain. The Committee considered the view of clinical specialists who informed the Committee that death was caused by factors such as age, acute infections, comorbidities and complications of Alzheimer's disease rather than the disease itself. The Committee noted that Alzheimer's disease affects predominantly, but not exclusively, people over 65 years of age. The Committee concluded that there was no evidence to suggest that the AChE inhibitors affected survival.

4.3.9 The Committee deliberated whether there was evidence that the AChE inhibitors lead to a delay in institutionalisation. The Committee acknowledged that time to institutionalisation was not generally included as an endpoint in randomised controlled trials and that published data were therefore limited. For example, the AD2000 study collected data on institutionalisation but limited accrual into the trial led to an underpowered conclusion about this outcome. The Committee considered the experiences of clinical specialists and patient experts, who reported that the following were often important factors in the

decision to move into institutionalised care: severe behavioural symptoms and the ability of the person with Alzheimer's disease and their family to cope with these, continence issues, and the availability of community support services. Opinion varied between the experts about the degree of impact of the AChE inhibitors on time to institutionalisation. Although one clinical specialist felt that prescribing these drugs has led to a significant delay in people with Alzheimer's disease entering institutions, others thought that this effect was small and many other factors were in operation (such as funding arrangements for state-funded residential care). The Committee was also aware of the individual variability of disease progression, which would influence at what stage a person with Alzheimer's disease would be admitted to an institution. The Committee concluded that although it was clinically plausible that treatment with an AChE inhibitor may delay time to institutionalisation, limited direct evidence was available to assess the size of this effect.

4.3.10 The Committee considered the evidence on adverse effects associated with the AChE inhibitors. The Committee acknowledged the gastrointestinal effects of these technologies. However, it concluded that the adverse effects of these technologies were well documented and that overall evidence since 2004 has not changed the tolerability profile of AChE inhibitors, apart from the fewer side effects noted in patients treated with rivastigmine patches than with oral rivastigmine.

Clinical effectiveness – memantine

4.3.11 The Committee considered the available evidence on the clinical effectiveness of memantine submitted by the Assessment Group, consultees and commentators. The Committee understood that memantine had a different mode of action from the AChE inhibitors and in practice would be used later in the treatment pathway in people with more severe Alzheimer's disease, this also being at a time when a higher proportion of people develop behavioural symptoms. It considered the new evidence available since the publication of NICE technology appraisal guidance 111, and the impact of the new evidence when it was combined with the data from the previous appraisal. The Committee noted that two of the randomised controlled trials included in the manufacturer's submission were excluded from the Assessment Group's

systematic review because at least 20% of each of the trial populations were people with mild Alzheimer's disease, which is not included in the current licensed indication of memantine.

4.3.12 The Committee considered the results of the new randomised controlled trials for memantine and the pooled results in order to estimate the size of clinical effectiveness for memantine compared with placebo or best supportive care. The Committee was aware of the limitations of the instruments used in the clinical trials including cognitive and behavioural scales. The Committee noted that although the new evidence considered by the Assessment Group did not substantially change the estimate of the clinical effectiveness of memantine compared with the review in 2004, the meta-analysis submitted by the manufacturer (which included individual patient data from trials with mixed populations so that the manufacturer was able to exclude data for patients with mild disease) showed significant benefits in the cognitive, functional, global and behavioural domains. The Committee concluded that memantine offers symptomatic benefit in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain.

4.3.13 The Committee considered the evidence in the manufacturer's submission on the clinical effectiveness of memantine in a subgroup of patients with agitation, aggression and/or psychotic symptoms, which are more common in patients with severe Alzheimer's disease. This evidence reported a statistically significant benefit of memantine for cognitive, functional and global outcomes and NPI score on agitation, aggression and/or psychotic symptoms in this subgroup. The Committee concluded, on the basis of the manufacturer's evidence and clinical specialist testimony, that memantine appears to have an effect on these symptoms.

4.3.14 The Committee considered the clinical effectiveness of memantine as an adjunct to AChE inhibitor treatment. The Committee noted evidence that showed no statistically significant benefit for combination treatment with memantine and AChE inhibitors for cognitive, functional, behavioural or global outcomes. The Committee was also made aware of ongoing trials for combination therapy including the DOMINO-AD (donepezil and memantine in moderate to severe Alzheimer's disease) study. The

Committee concluded that combination treatment with memantine and AChE inhibitors could not be recommended because of lack of evidence of additional clinical efficacy compared with memantine monotherapy.

4.3.15 The Committee considered the new evidence since 2004 of adverse effects associated with memantine and noted that some patients experience agitation that resolves when the drug is stopped, although agitation was also a main adverse event for those taking placebo. The Committee concluded that the adverse effects of memantine were well documented and that evidence since 2004 has not changed the tolerability profile.

Cost effectiveness

4.3.16 The Committee reviewed the two economic models submitted by the manufacturers of donepezil and memantine alongside the Assessment Group's model. The Committee considered that the key differences between the models included the selection of cohort data used to model disease progression, model structure (Markov compared with a discrete event simulation), the extent to which the model included the effectiveness of treatment for cognitive, functional and behavioural outcomes, and the measurement of patient utility based on patient or carer proxy values.

Cost effectiveness – donepezil, galantamine and rivastigmine

4.3.17 The Committee considered the most appropriate cohort data on which to model disease progression. The Committee heard from clinical specialists about the importance of using data from the UK compared with the US because of differences in the healthcare system, and differences in the management of Alzheimer's disease. The Committee also heard from clinical specialists that UK population data such as that found in the Wolstenholme dataset is the best available data on which to model progression of Alzheimer's disease because of the UK location, its long follow-up, the absence of pharmacological treatment for Alzheimer's disease and the availability of individual patient data. The Committee was aware of the limitations of this dataset including the small population, the relatively old data (collected between 1988 and 1999),

which might not reflect current rates of and times to institutionalisation, and the fact that the study was based in a semi-rural location. The Committee concluded that although the Wolstenholme dataset that formed the basis of the Assessment Group's model had these limitations it still represented the best available data.

4.3.18 The Committee considered the appropriateness of the structure of the Assessment Group's model, which was based on predicting time to institutionalisation. The Committee was aware that the uncertainty about time to institutionalisation was an issue that affected all submitted models. The Committee recognised the lack of institutionalisation data from randomised controlled trials, the limitations of the AD2000 study which collected institutionalisation data but was underpowered to measure this outcome, and the absence of a systematic review of observational studies available in this area. The Committee discussed the various definitions of institutionalisation. The Committee was aware that in clinical practice, the type of institution would have an impact on time to institutionalisation, as would cost and patient characteristics. The Committee was also aware that the Assessment Group had equated institutionalisation to severe disease, therefore assuming that AChE inhibitors would be stopped on entering an institution. However, the Committee acknowledged that in clinical practice, institutionalisation would not be based on disease severity alone. The Assessment Group used the definition of institutionalisation from the Wolstenholme cohort study, on which disease progression in its model was based.

4.3.19 The Committee considered that only the Assessment Group addressed the decision problem in the scope because it included all of the AChE inhibitors as comparators for mild to moderate Alzheimer's disease, whereas the manufacturer of donepezil's model compared donepezil with best supportive care only. The Committee concluded that there were limitations in constructing an economic model based on time to institutionalisation but that the Assessment Group's model was based on the best currently available and detailed UK evidence to evaluate the cost effectiveness of donepezil, galantamine and rivastigmine.

4.3.20 The Committee discussed the assumption in the Assessment Group's model that age, cognition and function were the key predictors of time to

institutionalisation. The Committee was aware of the limitations of scales such as the MMSE in evaluating severity of and change in Alzheimer's disease and also as a proxy for the delay in time to institutionalisation. The Committee also understood that the Wolstenholme study had used a scale of function that had been mapped to another index (the Barthel index), which in turn had been mapped by the Assessment Group to a commonly used index of activities of daily living. The Committee was aware of the potential uncertainties caused by these processes. However, considering all these factors in relation to cognitive and functional scales, the Committee considered it appropriate to use age, cognition and function as key predictors of time to institutionalisation. The Committee considered whether behavioural symptoms should also have been included as a predictor of time to institutionalisation in the Assessment Group's model. The Committee was aware that the Assessment Group's model did not incorporate this because of lack of data. The Committee noted that the clinical specialists and patient experts had emphasised behavioural symptoms being a key factor when deciding when to admit a person with Alzheimer's disease to an institution. The Committee noted that when behaviour was removed from the manufacturer of donepezil's model in sensitivity analyses, it did not have a big impact on the incremental cost-effectiveness results. The Committee concluded that although behaviour was a potential predictor of time to institutionalisation in everyday life, its omission from a model already including cognition and function was unlikely to substantially change the outputs of the model in mild and moderate Alzheimer's disease.

4.3.21 The Committee considered the importance of the assumption that there was no survival effect of treatment. The Committee considered the sensitivity analyses conducted by the Assessment Group, which had assumed a survival effect of 1.9–2.2 months and subsequently raised the ICERs for the AChE inhibitors to over £30,000 per QALY gained. The Committee understood that this increase in ICERs was expected. This was because when no survival effect was assumed (as per the base case), the delay in time to institutionalisation with treatment resulted in substantial savings in the costs that would have been incurred as a consequence of living in an institution. Assuming that there was also a survival benefit with treatment meant that the costs incurred from living

in an institution would be delayed, but not saved because people would live for longer. Therefore the incremental difference in costs was higher and the ICER increased. The Committee noted both the lack of randomised evidence measuring the survival effect of treatment with the AChE inhibitors and clinical opinion that mortality was more likely to be influenced by other factors unrelated to treatment. The Committee concluded that the assumption of no survival effect from treatment with the AChE inhibitors in the base-case model was appropriate in light of the lack of evidence of survival effect from randomised controlled trials.

4.3.22 The Committee considered the assumption of a 4% discontinuation rate of treatment in the Assessment Group's model. The Committee was aware that the Assessment Group's model included the ability to allow for discontinuation and this may have been one explanation for the difference in ICERs resulting from this model and the model used in NICE technology appraisal guidance 111 (the SHTAC model). The Committee considered how the Assessment Group had made the assumption of a constant rate of 4% based on the included randomised controlled trial evidence. For all effectiveness estimates it was assumed that an intention-to-treat analysis had been done, so that estimates related to all participants and not only those continuing on treatment. Given that many randomised controlled trials did not report an intention-to-treat analysis, this assumption was likely to over-estimate any treatment effects in the decision model. However, clinical specialists advised that discontinuation in clinical practice is between 2 and 5% per year and considered a 4% discontinuation rate to be appropriate. In addition, the Committee recognised that in sensitivity analyses, variation in the assumed discontinuation rate had the biggest impact on cost-effectiveness estimates. Increasing discontinuation rates led to fewer costs and greater net benefit for the AChE inhibitors and vice versa. The Committee concluded that it was appropriate to include discontinuation rates in the economic model and accepted that the assumption of 4% was plausible.

4.3.23 The Committee considered other inputs to the model, such as assumptions about the costs and QALYs generated in the pre-institutional and institutional health states of the Assessment Group's model. The Committee heard from the Assessment Group that the

monthly costs of pre-institutional care and institutional care were higher in its model than in the SHTAC model. When the delay in institutionalisation was taken into account (1.4 to 1.7 months in the Assessment Group's model), donepezil treatment (the example selected by the Assessment Group) in the Assessment Group's model was cost saving compared with best supportive care because the additional costs incurred in pre-institutional care (increased drug costs, monitoring costs and care costs) were outweighed by the cost saving associated with people spending less time in institutional care. In the same way, the QALYs gained by delaying the time to institutionalisation outweighed the QALYs lost in the institutional care health state in the Assessment Group's model.

4.3.24 The Committee was aware that the cost of institutionalisation varied according to institution type and the level of care needed, the availability of institutional care and support services, and that funding arrangements for residential care can result in significant individual contributions by the patient or family. The Committee considered it acceptable to use an average cost for institutional care and accepted the fixed cost of institutionalisation used in the Assessment Group's model. Based on information provided by clinical specialists and patient experts, the Committee also accepted the assumptions in the Assessment Group's model about costs of monitoring the patient every 6 months.

4.3.25 The Committee considered whether assumptions and inputs about health-related quality of life and utilities included in the Assessment Group's model were reasonable. The Committee heard that utility values for health-related quality of life reported by patients themselves and by carers as proxy responses were both relevant. The Committee heard from clinical specialists that in early stages of the disease it would be appropriate for the patient themselves to report their own outcomes, but in more severe stages of the disease a proxy utility provided by the carer would be appropriate. The Committee acknowledged that there were differences in the responses given by patients and those given by carers but that in sensitivity analyses conducted by the Assessment Group, changes to utility values had a small impact on ICERs. The Committee concluded that the assumptions and inputs about utilities in the Assessment Group's model were appropriate.

4.3.26 The Committee also considered the Assessment Group's approach to a variable cost and utility in the pre-institutionalisation health state. The Committee acknowledged that this was a difference between the Assessment Group and SHTAC models, and may have accounted for some of the differences in the ICERs produced by the two models.

4.3.27 The Committee considered whether there were differences in cost effectiveness for particular subgroups of people with Alzheimer's disease. The Committee reviewed the subgroup analyses conducted by the Assessment Group in mild and moderate Alzheimer's disease. The Committee noted that these had been provided as an exploratory analysis by the Assessment Group and that the Assessment Group's model assumed the same treatment effect for patients with mild and moderate disease. The Committee was aware that in NICE technology appraisal guidance 111 a difference in treatment effect between mild and moderate populations was assumed, on the basis of analysis by the Medical Research Council Biostatistics Unit. The Committee was also aware that no subgroup analyses had been identified as part of the systematic review of clinical effectiveness analysis. The Committee also noted that in clinical practice, clinicians found it difficult to differentiate between mild and moderate disease when using the MMSE. The Committee was also aware that many AChE inhibitor trials included patients with both mild and moderate disease.

4.3.28 The Committee considered the merits of the Assessment Group's model compared with the manufacturer of donepezil's model. The Committee considered that both models captured the costs and benefits of treatment with greater accuracy than the SHTAC model used in the previous appraisal and that the manufacturer's discrete event simulation model offered an intuitive description of the disease. The Committee considered the enhancements in the Assessment Group's model compared with the SHTAC model and noted that the individual patient data on which disease progression in the Assessment Group's model was based, combined with the differential utility and costs accrued in the pre-institutional health state, led to a more accurate representation of the costs and outcomes of treatment. The Committee further noted that the discrete event simulation model provided by the manufacturer of donepezil (based on a US cohort) was unable to adequately compare all

available treatment options within a full incremental analysis. Overall, the Committee preferred the Assessment Group's model over the discrete event simulation model because the modelling of disease progression (based on UK data from patients who had not received treatment with AChE inhibitors) was most appropriate for the UK clinical setting and the model enabled all of the treatments to be compared in a full incremental analysis. The Committee noted, however, that the manufacturer's model was useful to enable comparisons for specific parts of the decision problem and to test the inputs, assumptions and face validity of the Assessment Group's model. Both models showed donepezil to be cost saving.

4.3.29 The Committee considered the base-case results for the cost effectiveness of the AChE inhibitors compared with best supportive care. The Committee noted that the key driver of cost effectiveness in the Assessment Group's model was treatment leading to delay to institutionalisation. This assumption led to less time spent in institutional care and subsequent savings to the NHS/personal social services. The Committee considered that, with this assumption, the Assessment Group's model demonstrated that each of the AChE inhibitors was cost saving compared with best supportive care.

4.3.30 The Committee noted the small difference in absolute costs and benefits between the AChE inhibitors. It also observed that small changes in some of the inputs and assumptions had significant impacts on the incremental estimates of cost effectiveness. The Committee concluded that overall, the AChE inhibitors donepezil, galantamine and rivastigmine had small but demonstrable clinical benefits and were cost-effective treatment options. The Committee concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of cost effectiveness and that therefore the best use of NHS resources would be the technology with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). The Committee further accepted that an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions (details of which can be found in the individual summaries of product characteristics) and

dosing profiles.

Cost effectiveness – memantine

4.3.31 The Committee considered the two models for the cost effectiveness of memantine presented by the manufacturer and the Assessment Group. It noted that although the structures of the models were similar, there were differences in the assumptions underlying the two models. The Committee considered that all the uncertainties about the assumptions and inputs in the Assessment Group's model for the AChE inhibitors also applied to the memantine model. However, the Committee identified additional uncertainties relating to memantine, such as estimates of treatment effect used in the models. The Committee considered the key differences between the Assessment Group's and manufacturer's models to be the selection of cohort data used to model disease progression, assumptions about the proportion of patients who were institutionalised at the start of treatment, the effectiveness estimates used in the model, and whether the model included the effectiveness of treatment on behavioural symptoms.

4.3.32 The Committee considered the cohort data on which disease progression in each of the models was based. The Committee was aware that the manufacturer's model used LASER-AD data to model disease progression, which had shorter follow-up compared with the cohort study used by the Assessment Group. It was also aware that many of the participants of the LASER-AD study were on active treatment. The Committee concluded that the Wolstenholme data used in the Assessment Group's model were more suitable for assessing disease progression because this study had longer follow-up and the participants were not receiving active therapies.

4.3.33 The Committee considered the assumptions included in the Assessment Group's model. The Committee acknowledged that some of the assumptions may have led to underestimates of the benefits of memantine compared with best supportive care. In the Assessment Group's model, for the 40% of patients with severe Alzheimer's disease who started in institutions or started with a low utility, there was limited opportunity to benefit from treatment, but they nevertheless accrue

costs. The Committee therefore concluded that the cost effectiveness of memantine may have been underestimated in the Assessment Group's model for patients with severe Alzheimer's disease, although by how much is uncertain.

4.3.34 The Committee considered the appropriateness of including the impact of memantine on behavioural outcomes. The Committee was aware that the Assessment Group had not included behavioural outcomes as a predictor of time to institutionalisation in its model but the model submitted by the manufacturer of memantine had included behaviour as a predictor of time to full-time care. The Committee noted that the manufacturer's model used LASER-AD data to model disease progression, which included the effectiveness of treatment on behavioural symptoms. The Committee heard from the Assessment Group that when the impact of memantine on behavioural symptoms was removed from the manufacturer's model it had little impact on the cost effectiveness of memantine compared with best supportive care. The Committee was also aware, based on the evidence from the patient experts and clinical specialists, that behavioural outcomes were not well captured by the instruments used in clinical trials. The Committee concluded that although behaviour is a potential predictor of time to institutionalisation, not including it in the Assessment Group's model was unlikely to substantially change its outputs for people with moderate to severe Alzheimer's disease.

4.3.35 The Committee also noted that the manufacturer's submission included a subgroup analysis of the cost effectiveness of memantine in a subgroup of patients with aggression, agitation and/or psychotic symptoms. The Committee heard from clinical specialists and the manufacturer that memantine appears to have cognitive, functional, global and behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms, which are more common in people with severe Alzheimer's disease. The Committee accepted that memantine may therefore have the potential to reduce the need for antipsychotics but noted that there was no randomised controlled trial evidence supporting this assumption. The Committee accepted on the basis of the evidence in the manufacturer's submission and expert testimony that memantine may offer benefit to people with severe Alzheimer's disease.

4.3.36 The Committee considered the estimates of treatment effect for memantine in the manufacturer's and Assessment Group's models. The Committee noted that estimates of treatment effect were different between the models. The Committee understood that the effectiveness data in the manufacturer's submission were based on a pooled estimate of memantine monotherapy and combination therapy with AChE inhibitors, whereas the Assessment Group's model included effectiveness estimates only for memantine monotherapy. The Committee also noted that the manufacturer's submission was based on analysis of individual patient data of people with moderate Alzheimer's disease taken from two randomised controlled trials that had been submitted to the European Medicines Agency (EMA) in order to gain the license extension for memantine in moderate disease. These data had not been included in the Assessment Group's report because more than 20% of the study population in the trials had mild Alzheimer's disease, and so did not fit with the inclusion criteria of the systematic review based on the licensed indications in the decision problem. As a consequence, the Committee found it difficult to reconcile the lack of statistically significant benefit seen in the meta-analysis from the Assessment Group for cognitive, functional and behavioural outcomes with the significant improvements (particularly for behaviour) in the manufacturer's individual patient data analyses. The Committee was uncertain about how much the difference in clinical effectiveness influenced the differences in cost-effectiveness results between the two models. It was also aware, based on the evidence provided by patient experts and clinical specialists, that behaviour was an important factor when considering institutionalisation. However, published evidence was limited because in trials, institutionalisation was not an outcome measure and instruments had limited capacity to capture behavioural changes. The Committee concluded that because the Assessment Group's model did not include results from some trials in the estimate of treatment effect for which access to individual patient data was needed, it may have underestimated the cost effectiveness of memantine, although by how much is uncertain.

4.3.37 Taking the above factors into account, the Committee considered that, on balance, the Assessment Group's model provided a suitable basis for decision making. This was because the cohort data used to model

disease progression were generalisable to the UK, the effectiveness data for memantine monotherapy and combination therapy with AChE inhibitors were not combined, and the cost effectiveness of memantine could be compared with that of the AChE inhibitors in moderate Alzheimer's disease.

4.3.38 The Committee considered that the base-case ICER for memantine of £32,100 per QALY gained compared with best supportive care in moderate to severe Alzheimer's disease was likely to be an overestimate of the true cost per QALY gained, although the size of this overestimation was uncertain. The Committee noted that in moderate disease there were active comparators, whereas only memantine has a marketing authorisation for severe disease.

4.3.39 The Committee considered the subgroups of people with moderate Alzheimer's disease only and severe Alzheimer's disease only. The Committee noted that in the Assessment Group's exploratory analysis, memantine dominated best supportive care for the moderate group, and for the severe group the ICER for memantine compared with best supportive care was £26,500 per QALY gained. The Committee also noted that both subgroup ICERs were lower than the combined base-case ICER of £32,100 per QALY. The Committee heard from the Assessment Group that this may be because of the different assumptions in the subgroup analysis compared with the base case.

4.3.40 The Committee concluded that memantine would not be cost effective compared with the AChE inhibitors in people with moderate disease because it generated fewer QALYs at a higher cost. The Committee noted that the use of memantine in the subgroup with moderate disease would represent a cost-effective use of NHS resources only if best supportive care was the comparator. It concluded that in people with moderate Alzheimer's disease memantine should be recommended for people who are intolerant of or have contraindications to AChE inhibitors.

4.3.41 The Committee thought that memantine was likely to have a positive effect on the quality of life of people with severe disease, because they are more likely to experience behavioural symptoms. This was not captured in the Assessment Group's model. Also, even though

behavioural benefit did not appear to have a great impact on the results of the manufacturer's model, the Committee had heard from clinical specialists that behavioural effect may not be well captured in the available evidence. The Committee considered that, had it been possible to include the behavioural benefit of memantine in the Assessment Group's model, the ICER would be less than £26,500 per QALY gained. It therefore concluded that treatment with memantine represented a cost-effective use of NHS resources for people with severe Alzheimer's disease.

Other issues

4.3.42 The Committee considered the criteria for recommending the AChE inhibitors in NICE technology appraisal guidance 111.The Committee acknowledged the importance of people with Alzheimer's disease being assessed by a specialist clinician and heard from clinical specialists that treatment with AChE inhibitors and memantine should always be initiated by a clinical specialist in accordance with the recommendations of NICE technology appraisal guidance 111. However, the Committee acknowledged that for assessing whether treatment should be continued, review by a specialist may be substituted by a shared care arrangement because this may put less pressure on local resources while still ensuring optimal treatment for patients.

4.3.43 The Committee also considered the recommendations of NICE technology appraisal guidance 111 for specific groups of people with Alzheimer's disease, such as those with disabilities (for example, sensory impairments) or linguistic or other communication difficulties. The Committee acknowledged comments from local NHS trusts that use of scales such as the MMSE made prescription monitoring and clinical audit less problematic. However, the Committee confirmed that, as in NICE technology appraisal guidance 111, when using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities or communication difficulties that could affect the results and make any adjustments they consider appropriate. The Committee noted comments received in consultation that assessment scales such as the MMSE may not capture the severity of disease or benefit of treatment in people with

a high level of education. It was aware that this group of people does not fall under the groups protected by equality legislation, but concluded that clinicians should also keep this in mind when assessing patients. Clinicians should also 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.

4.3.44 The Committee discussed the continuation of treatment and thought it appropriate that treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms. The Committee considered comments received during consultation that a recommendation of 6-monthly reviews for treatment continuation was not evidence based and could be a misuse of NHS resources. The Committee acknowledged that among the submitted data, there was insufficient evidence to define an optimal review time although most clinical-effectiveness evidence was from 6-month trials and the economic models included the costs of 6-monthly monitoring. The Committee also assumed that good clinical practice would be to regularly review patients. The Committee considered that making recommendations on the timings of patient reviews and other implementation issues, such as switching from AChE inhibitors to memantine according to the recommendations, might be better addressed by the clinician. It concluded that patients who continue on the drug should be reviewed regularly using cognitive, global, functional and behavioural assessment and that treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care. The Committee further concluded that carers' views on the patient's condition at follow-up should be sought.

Summary of the Appraisal Committee's key conclusions

TA217	Appraisal title: Donezepil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111)	Section

Key conclusion	
The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine are recommended as options for managing mild to moderate Alzheimer's disease.	1.1
The Committee noted that the key driver of cost effectiveness in the Assessment Group's model was treatment leading to delay to institutionalisation. The Committee considered that, with this assumption, the Assessment Group's model demonstrated that each of the AChE inhibitors was cost saving compared with best supportive care.	4.3.29
The Committee concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of cost effectiveness and that therefore the best use of NHS resources would be the technology with the lowest acquisition cost. The Committee further accepted that an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations around adherence, medical comorbidity, possibility of drug interactions and dosing profiles.	4.3.30
Memantine is recommended as an option for managing Alzheimer's disease for people with moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors, or for people with severe Alzheimer's disease.	1.2
The Committee concluded that memantine would not be cost effective compared with the AChE inhibitors in people with moderate disease because it generated fewer QALYs at a higher cost. The Committee noted that the use of memantine in the subgroup with moderate disease would represent a cost-effective use of NHS resources only if best supportive care was the comparator.	4.3.40
With regard to the severe subgroup analysis, the Committee considered that, had it been possible to include the behavioural benefit of memantine in the Assessment Group's model, the ICER would be less than £26,500 per QALY gained. It therefore concluded that treatment with memantine represented a cost-effective use of NHS resources for people with severe Alzheimer's disease.	4.3.41
Current practice	

Clinical need of patients including the availability of alternative treatments	The Committee was aware that there is currently no cure for Alzheimer's disease and that the AChE inhibitors and memantine treat the symptoms of Alzheimer's disease but do not slow the progression of the disease.	4.3.2
The technology		
Proposed benefits of the technology	The Committee concluded that new evidence provided additional support to the conclusions from 2004 that each of the AChE inhibitors offers benefits over best supportive care for cognitive, functional and global outcomes, and may offer some benefit in behavioural outcomes, although the nature and extent of behavioural benefits are uncertain.	4.3.5
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition?)	The Committee concluded that memantine offers symptomatic benefit in cognitive, functional, global and behavioural outcomes, although the size of the benefit is uncertain.	4.3.12

What is the position of the treatment in the pathway of care for the condition?	The Committee considered the current management of Alzheimer's disease under the recommendations of NICE technology appraisal guidance 111, which recommends AChE inhibitors for the treatment of moderate Alzheimer's disease. The Committee was aware of both the importance of early diagnosis and carer and clinical views on the advantages of early use of AChE inhibitors in the treatment of Alzheimer's disease. The Committee heard from clinical specialists that there is variation in clinical practice and that AChE inhibitors are also used to treat some patients with an MMSE score of above 20. Memantine is not recommended by NICE technology appraisal guidance 111 except in the context of clinical trials.	4.3.2
Adverse effects	The Committee stated that the adverse effects of AChE inhibitors and memantine are well documented and that overall evidence since 2004 has not changed the tolerability profile of these treatments.	4.3.10 4.3.15
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee stated that a small amount of new evidence about the clinical effectiveness of the AChE inhibitors from randomised controlled trials had been published since 2004.	4.3.4
	The Committee considered the results of the new randomised controlled trials for memantine and the pooled results in order to estimate the size of clinical effectiveness for memantine compared with placebo or best supportive care. The Committee noted that although the new evidence considered by the Assessment Group did not substantially change the estimate of the clinical effectiveness of memantine compared with the review in 2004, the meta-analysis submitted by the manufacturer showed significant benefits.	4.3.12

Relevance to general clinical practice in the NHS	The Committee recognised the heterogeneity of outcome measures in trials and was aware of the limitations of some of the instruments used in the clinical trials, including cognitive and behavioural scales.	4.3.4
Uncertainties generated by the evidence	The Committee concluded that AChE inhibitors may offer some behavioural benefits although their nature and extent are uncertain owing to mixed results from available evidence.	4.3.5
	The Committee concluded that although there was no evidence available on health-related quality of life from a systematic review of randomised controlled clinical trials, there was some anecdotal evidence from clinical practice of benefits to patients and carers from using AChE inhibitors.	4.3.7
	The Committee concluded that there was no evidence to suggest that the AChE inhibitors affected survival.	4.3.8
	The Committee concluded that memantine offers symptomatic benefit in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain.	4.3.12
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered whether there were differences in cost effectiveness for particular subgroups of people with Alzheimer's disease. The Committee noted that the Assessment Group's model assumed the same treatment effect for patients with mild and moderate disease. The Committee was aware that in NICE technology appraisal guidance 111 a difference in treatment effect between mild and moderate populations was assumed in the amended base case, on the basis of analysis by the Medical Research Council Biostatistics Unit. The Committee was also aware that no subgroup analyses had been identified as part of the systematic review of clinical effectiveness analysis.	4.3.27

	The Committee accepted on the basis of the evidence in the manufacturer's submission and expert testimony that memantine may offer benefit to people with severe Alzheimer's disease.	4.3.35
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that new evidence provided additional support to the previous conclusions from 2004 that each of the AChE inhibitors offers benefits over best supportive care for cognitive, functional and global outcomes, and may offer some benefit in behavioural outcomes, although the nature and extent of behavioural benefits are uncertain owing to mixed results from the available evidence.	4.3.5
	The Committee concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of clinical effectiveness.	4.3.6
	The Committee concluded that memantine offers symptomatic benefit in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain.	4.3.12
	The Committee concluded that combination treatment with memantine and AChE inhibitors could not be recommended because there is a lack of evidence of additional clinical efficacy compared with monotherapy.	4.3.14
Evidence for cost effectiveness		
Availability and nature of cost effectiveness evidence	The Committee considered economic models from the Assessment Group, the manufacturer of donepezil and the manufacturer of memantine.	4.3.16

	The Committee considered that only the Assessment Group addressed the decision problem in the scope because it included all of the AChE inhibitors as comparators for mild to moderate Alzheimer's disease, whereas the manufacturer of donepezil's model compared donepezil with best supportive care only. The Committee concluded that there were limitations in constructing an economic model based on time to institutionalisation but that the Assessment Group's model was based on the best currently available and detailed UK evidence to evaluate the cost effectiveness of donepezil, galantamine and rivastigmine.	4.3.19
	The Committee considered that, on balance, the Assessment Group's model provided a suitable basis for decision making. This was because the cohort data used to model disease progression were generalisable to the UK, the effectiveness data for memantine monotherapy and combination therapy with AChE inhibitors were not combined, and the cost effectiveness of memantine could be compared with that of the AChE inhibitors in moderate Alzheimer's disease.	4.3.37
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was aware of the limitations of the Wolstenholme dataset including the small population, the relatively old data (collected between 1988 and 1999), which might not reflect current rates of and times to institutionalisation, and the fact that the study was based in a semi-rural location. The Committee concluded that although the Wolstenholme dataset that formed the basis of the Assessment Group's model had these limitations it still represented the best available data.	4.3.17

	The Committee concluded that the assumption of no survival effect from treatment with the AChE inhibitors in the base-case model was appropriate in light of the lack of evidence of survival effect from randomised controlled trials.	4.3.21
	The Committee concluded that although behaviour was a potential predictor of time to institutionalisation, not including it in the Assessment Group's model (which already included cognition and function) was unlikely to substantially change the outputs of the model in mild, moderate and severe Alzheimer's disease.	4.3.20 4.3.34
Incorporation of health-related quality-of-life benefits and utility values. Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee considered whether assumptions and inputs about health-related quality of life and utilities included in the Assessment Group's model were reasonable. The Committee acknowledged that there were differences in the responses given by patients and those given by carers when reporting outcomes, but that in sensitivity analyses conducted by the Assessment Group, changes to utility values had a small impact on ICERs. The Committee concluded that the assumptions and inputs about utilities in the Assessment Group's model were appropriate.	4.3.25
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee did not consider subgroups for AChE inhibitors.	
	The Committee noted that the use of memantine in the subgroup with moderate disease would represent a cost-effective use of NHS resources only if best supportive care was the comparator (that is, for people with moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors).	4.3.40

	The Committee concluded that treatment with memantine represented a cost-effective use of NHS resources for people with severe Alzheimer's disease.	4.3.41
What are the key drivers of cost effectiveness?	The Committee considered the appropriateness of the structure of the Assessment Group's model, which was based on predicting time to institutionalisation.	4.3.18
	Considering all the factors in relation to cognitive and functional scales, the Committee considered it appropriate to use age, cognition and function as key predictors of time to institutionalisation. The Committee concluded that although behaviour was a potential predictor of time to institutionalisation in everyday life, its omission from a model already including cognition and function was unlikely to substantially change the outputs of the model in mild and moderate Alzheimer's disease.	4.3.20
	The Committee noted that the key driver of cost effectiveness in the Assessment Group's model was treatment leading to delay to institutionalisation	4.3.29
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that, with the assumption that the key driver of cost effectiveness in the Assessment Group's model was treatment leading to delay to institutionalisation, the Assessment Group's model demonstrated that each of the AChE inhibitors was cost saving compared with best supportive care.	4.3.29

	The Committee noted the small difference in absolute costs and benefits between the AChE inhibitors. It also observed that small changes in some of the inputs and assumptions had significant impacts on the incremental estimates of cost effectiveness. The Committee concluded that overall, the AChE inhibitors donepezil, galantamine and rivastigmine had small but demonstrable clinical benefits and were cost-effective treatment options. The Committee concluded that there was insufficient evidence to differentiate between the AChE inhibitors in terms of cost effectiveness and that therefore the best use of NHS resources would be the technology with the lowest acquisition cost.	4.3.30
	The Committee considered that the base-case ICER for memantine of £32,100 per QALY gained compared with best supportive care in moderate to severe Alzheimer's disease was likely to be an overestimate of the true cost per QALY gained, although the size of this overestimation was uncertain. The Committee noted that in the Assessment Group's exploratory analysis, memantine dominated best supportive care for the moderate group, and for the severe group the ICER for memantine compared with best supportive care was £26,500 per QALY gained. The Committee concluded that memantine would not be cost effective compared with AChE inhibitors in people with moderate disease because it generated fewer QALYs at a higher cost.	4.3.38 4.3.39 4.3.40
	The Committee considered that, had it been possible to include the behavioural benefit of memantine in the Assessment Group's model, the ICER would be less than £26,500 per QALY gained for severe disease. It therefore concluded that treatment with memantine represented a cost-effective use of NHS resources for people with severe Alzheimer's disease.	4.3.41

Additional factors taken into account		
Patient access schemes (Pharmaceutical Price Regulation Programme)	Not applicable	
End-of-life considerations	Not applicable	
Equalities considerations, Social Value Judgement	The Committee confirmed that, as in NICE technology appraisal guidance 111, when using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities or communication difficulties that could affect the results and make any adjustments they consider appropriate. Clinicians should also 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.	4.3.43
	The Committee recognised the difficulties of using MMSE score alone to assess the severity of Alzheimer's disease and the response to AChE inhibitors. The Committee agreed that cognitive scales alone such as the MMSE are not always appropriate for assessing the severity of dementia. The Committee concluded that if cognitive scales are not appropriate for assessing the need for treatment, or whether to continue treatment, then clinicians should use another appropriate method of assessment.	4.3.3

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has Alzheimer's disease and the doctor responsible for their care thinks that donepezil, galantamine, rivastigmine or memantine is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 Research is needed to generate robust and relevant data on the effects of treating people with Alzheimer's disease on both short-term and long-term outcomes, disease progression through relevant health states, and quality of life.

6.2 Research is needed on the impact of treating Alzheimer's disease on mortality and institutionalisation, and to assess the relationship between disease progression and carer utility (quality of life).

7 Related NICE guidance

- Dementia: assessment, management and support for people living with dementia and their carer (2018) NICE guideline NG97

8 Review of guidance

8.1 The guidance on this technology will be considered for review by the Guidance Executive in April 2014. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
March 2011

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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 Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Brian Buckley
Lay member

Professor Usha Chakravarthy
Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Ian Davidson
Lecturer in Rehabilitation, The University of Manchester

Professor Simon Dixon
Senior Lecturer in Health Economics, University of Sheffield

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology

Gillian Ells
Prescribing Advisor, NHS Sussex Downs and Weald

Dr Jon Fear
Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh
Senior Lecturer and Honorary Consultant, University of Liverpool

Niru Goenka
Consultant Physician, Countess of Chester NHS Foundation Trust

Susan Griffin
Research Fellow, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Alison Hawdale
Lay member

Professor John Hutton
Professor of Health Economics, University of York

Professor Peter Jones
Pro Vice Chancellor for Research & Enterprise, Keele University
Professor of Statistics, Keele University

Dr Steven Julious

Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Rachel Lewis
Doctoral Researcher

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor Jonathan Michaels (Vice Chair)
Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner
General Medical Practitioner, Tramways Medical Centre

Professor Femi Oyebode
Professor of Psychiatry & Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge
GP and Consultant in Medicines Management, NHS Lothian

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital

Paddy Storrie
Lay member

Charles Waddicor
Chief Executive, NHS Berkshire

Dr Lok Yap
Consultant in Acute Medicine & Clinical Pharmacology, Whittington Hospitals NHS Trust

B Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

- Tim Kendall, National Collaborating Centre for Mental Health

C 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.

Jennifer Priaulx
Technical Lead

Eleanor Donegan and Rebecca Trowman
Technical Advisers

Kate Moore
Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG):

- Bond M, Rogers G, Peters J et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111): a systematic review and economic model, June 2010.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturers/sponsors:

- Eisai/ Pfizer
- Lundbeck
- Novartis
- Shire

II) Professional/specialist and patient/carer groups:

- Alzheimer's Society
- Brunelcare
- The Neurological Alliance
- Association of British Neurologists
- British Geriatrics Society

- Royal College
- Royal of Physicians
- Royal of Psychiatrists

III) Other consultees:

- Department of Health
- NHS Islington
- NHS West Kent
- Welsh Assembly Government

IV) Commentator organisations (without the right of appeal):

- NHS Quality Improvement Scotland
- Eisai/Pfizer
- Lundbeck
- Novartis
- Shire
- Institute for Ageing and Health
- Research Institute for the Care of Older People
- Peninsula Technology Assessment Group, University
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Mental Health

B. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. 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, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of technology appraisal guidance 111) by attending the initial Committee discussion and/or

providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Anthony Bayer, Senior Lecturer in Geriatric Medicine, nominated by British Geriatrics Society – clinical specialist
- Dr Peter Connelly, Consultant Old Age Psychiatrist, nominated by NHS Quality Improvement Scotland – clinical specialist
- Andrew Chidgey, Head of Policy and Public Affairs, Alzheimer's Society, nominated by Alzheimer's Society – patient expert
- Chris Hill, nominated by Alzheimer's society – patient expert
- Henry Simmons, Chief Executive, Alzheimer Scotland, nominated by NHS Quality Improvement Scotland – patient expert

C. The following individuals were nominated as NHS Commissioning experts by the selected NHS Trust allocated to this appraisal. They gave their expert/NHS commissioning personal view on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Edwina Affie, Assistant Director Public Health, NHS Islington, selected by NHS Islington – NHS Commissioning expert
- Amelia Stecher, Assistant Director of Care Standards/Acting IFR Lead, NHS West Kent, selected by NHS West Kent – NHS Commissioning expert

D. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Eisai/ Pfizer
- Lundbeck
- Novartis
- Shire

Update information

June 2018: Recommendations 1.1 and 1.2 have been amended to clarify that they refer to monotherapy. Recommendation 1.3 has been updated and replaced by recommendation 1.5.5 in the NICE guideline on dementia.

May 2016: Recommendation 1.3 in this technology appraisal has been partially updated by recommendation 1.6.2.3 in the NICE guideline on dementia (NICE guideline CG42). Specifically:

- non-specialists can now prescribe donezepil, galantamine, rivastigmine and memantine, as long as they have taken advice from a clinician who has the necessary knowledge and skills. This includes:
  - secondary care medical specialists such as psychiatrists, geriatricians and neurologists
  - other healthcare professionals such as GPs, nurse consultants and advanced nurse practitioners with specialist expertise in diagnosing and treating Alzheimer's disease
- local arrangements for prescribing, supply, and treatment review should follow the NICE guideline on medicines optimisation (NICE guideline NG5).

February 2014: Implementation section updated to clarify that donepezil, galantamine, rivastigmine and memantine are recommended as options for treating Alzheimer's disease. Additional minor maintenance update also carried out.

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Accreditation