

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

**SUBMISSION OF EVIDENCE PREPARED
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GLOSSARY

ACHEI	Acetylcholinesterase Inhibitor
AD	Alzheimer's Disease
ADAS-cog	Cognitive Subscale of Alzheimer's Disease Assessment Scale
ADCS-ADL ₂₃	Alzheimer's Disease Cooperative Study Activities of Daily Living
ADCS-ADL ₁₉	Alzheimer's Disease Cooperative Study Activities of Daily Living (a modified 19-item inventory for patients with more advanced AD)
ADCS-CGI-C	Alzheimer's Disease Cooperative Study Clinical Global Impression of Change
ADI	Alzheimer's Disease International
AE	Adverse Event
AHEAD	Assessment of Health Economics in Alzheimer's Disease
ANCOVA	Analysis of Covariance
AP	Antipsychotics
APA	American Psychiatric Association
APS	Agitation/Aggression and/or Psychotic Symptoms
BADL	Basic Activities of Daily Living
BAP	British Association for Psychopharmacology
BDS	Behaviourally Disturbed Subpopulation
BNF	British National Formulary
BPSD	Behavioural and Psychological Symptoms of Dementia
CEAC	Cost-Effectiveness Acceptability Curves
CIBIC-Plus	Clinician's Interview-Based Impression of Change Plus Caregiver Input
CSRI	Client Service Receipt Inventory
CT	Computerised Tomography
DART-AD	Dementia Antipsychotic Withdrawal Trial
DoH	Department of Health
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimension
EURODEM	European Community Concerted Action Epidemiology of Dementia
FDA	Food and Drug Administration
FTC	Full-Time Care
GP	General Practitioner
HTA	Health Technology Assessment
HRQoL	Health Related Quality of Life
HSQ-12	Health Status Questionnaire – 12 item
IADL	Instrumental Activities of Daily Living
ITT	Intention to Treat
LASER-AD	London and the South-East Region Alzheimer's Disease
LOCF	Last Observation Carried Forward
MMSE	Mini-Mental State Examination
ND-IFD	Non-dependent but with instrumental functional disability
NAO	National Audit Office
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMDA	N-Methyl D-Aspartate
NOSGER	Nurses' Observation Scale for Geriatric Patients
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory-Nursing Home
NPS	Neuropsychiatric symptoms
NSF	National Service Framework
OC	Observed Cases
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit

PSUR	Periodic Safety Update Report
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QoL-AD	Quality of Life in Alzheimer's Disease
RCT	Randomised Controlled Trial
SHTAC	Southampton Health Technology Assessment Centre
SIB	Severe Impairment Battery
SMD	Standardised Mean Difference
SPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event

TABLE OF CONTENTS

1.0	Executive Summary	6
2.0	Background Section	9
2.1.	Clinical Characteristics of Alzheimer's Disease (AD)	9
2.2	Assessment Tools in AD	10
2.3	Epidemiology	11
2.3.1	Prevalence of Alzheimer's Disease in the UK	11
2.3.2	Prevalence of Agitation, Aggression and Psychosis	11
2.4	Burden of Disease	11
2.5	Current Disease Management	12
2.5.1	AChEIs	12
2.5.2	Memantine	13
2.5.3	Antipsychotic Use in AD Patients	13
2.5.4	Treatment Guidelines	13
2.6	Place of Memantine in the Treatment Programme for AD in the UK	14
2.7	Description of the Decision Problem	15
3.0	Clinical Effectiveness of Memantine	16
3.1	Memantine in Moderate to Severe AD	16
3.1.1	Methods	16
3.1.2	Results	18
3.1.3	Clinical Relevance of Efficacy of Memantine in Moderate to Severe AD	19
3.2	Memantine in Sub-group of Moderate to Severe AD Patients with Agitation/Aggression and/or Psychotic Symptoms (APS Sub-group)	22
3.2.1	Methods	22
3.2.2	Results	23
3.3	Other Supporting Evidence	26
3.3.1	Indirect Comparison of Risperidone and Memantine	26
3.3.2	MAG-D Study	26
3.4	Real-life Effectiveness of Memantine in AD	27
3.5	Safety	28
3.6	Discussion	29
4.0	Cost Effectiveness	30
4.1	Statement of Problem and Rationale for Modelling Approach	30
4.2	Model Structure	31
4.2.1	Comparator	31
4.2.2	Model Structure	31
4.2.3	Population	32
4.2.4	Study Perspective	32

4.2.5	Time Horizon and Discounting	32
4.2.6	Duration of Treatment Administration and Treatment Effect	33
4.2.7	Implementation of the Model	33
4.3	Model Inputs.....	33
4.3.1	Main Effectiveness Data Sources.....	33
4.3.2	Transition Probabilities	34
4.3.3	Utility.....	34
4.3.4	Costs	35
4.4	Analyses.....	36
4.4.1	Parameter Uncertainty	36
4.4.2	Deterministic Scenario Analyses	36
4.5	Results	37
4.5.1	Base Case Results.....	37
4.5.2	Sensitivity Analyses.....	37
4.6	Discussion.....	41
4.7	Implications of Model Results	44
5.0	Wider Implications.....	45
5.1	Budget Impact	45
5.1.1	Eligible Population.....	45
5.1.2	Annual Drug Costs	46
5.1.3	Budget Impact Scenarios	46
5.2	Service Impact	49
5.2.1	Implementation of New Guidelines in Moderate to Severe Patients Have Minimal Net Impact.....	49
5.2.2	Positive Service Impact.....	49
5.3	Wider Considerations.....	49
5.3.1	Introduction.....	49
5.3.2	Age	50
5.3.3	Individual Choice	50
5.3.4	Conditions Associated with Stigma	50
5.3.5	Avoiding Discrimination and Promoting Equality.....	51
5.3.6	Disability/Quality of Life	52
5.4	Conclusions.....	52
5.4.1	Why AD in General Deserves Special Consideration.....	52
5.4.2	Why Memantine Deserves Special Consideration	52
6.0	References	54

LIST OF TABLES

Table 2.1.	EURODEM prevalence rates of diagnosed and undiagnosed dementia in the UK by age ⁴¹	11
Table 3.1.	Summary of efficacy of memantine on standard AD endpoints in patients with moderate to severe AD, intention-to-treat population, observed cases (OC) approach, 24/28 weeks	18
Table 3.2.	Proportion of patients with any clinical worsening and marked clinical worsening, moderate to severe AD population, OC, week 24/28	20
Table 3.3.	Description of baseline characteristics per sub-group	24
Table 3.4.	Summary of meta-analyses results in patients with APS and remaining patients	24

Table 3.5. Difference in evolution of clinical assessments between sub-groups per treatment....	25
Table 3.6. Summary of evidence from observational “real life” studies	27
Table 4.1. Memantine effect in the model.....	34
Table 4.2. Total monthly cost per health state	35
Table 4.3. Base case result – overall population with moderate to severe AD	37
Table 4.4. Base case result – APS	37
Table 4.5. Base case result probabilistic – overall population with moderate to severe AD	38
Table 4.6. Summary of sensitivity analyses – overall population.....	39
Table 4.7. Base case results probabilistic - APS	40
Table 4.8. Summary of sensitivity analyses - APS	41
Table 4.9. Health utilities between dependency and non-dependency states	42
Table 5.1. Estimated patient numbers by year	46
Table 5.2. Budget impact of different uptake scenarios.....	48

LIST OF FIGURES

Figure 2.1. Memantine target population	14
Figure 3.1. Evolution of cognition per treatment and patient profile.....	26
Figure 4.1. Model schematic.....	32
Figure 4.2. Cost-effectiveness scatter plot in overall population with moderate to severe AD	38
Figure 4.3. Cost-effectiveness scatter plot in the APS sub-group	40

1.0 EXECUTIVE SUMMARY

Burden of disease

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder, which affects an estimated 380,000 people in England and Wales. Prevalence increases dramatically with age. The incidence rate of AD has been estimated at 4.9 per 1000 people years in individuals over 65 years in the UK, with women carrying a higher risk.

AD is characterised by a progressive loss of cognitive and intellectual function, the ability to perform the activities of daily living, as well as the emergence of a range of behavioural and psychological symptoms. The progression of AD is conventionally divided into three stages - mild, moderate and severe - based on the domains of cognition, function, behaviour and global status. The median survival period from the diagnosis of AD is approximately 6 years (range 1–16 years), with approximately one-third of the time spent in the severe stage of disease. A large proportion of patients are estimated to be in the moderate (31%) and severe (21%) disease stages at any one time.

The clinical spectrum of AD resides on a continuum and rates of decline vary widely, although behavioural and psychological symptoms usually advance with increased frequency and severity with disease progression. The moderate to severe stages of AD are characterised by the emergence and worsening of psychotic and behavioural symptoms, especially agitation and aggression. Psychosis affects more than 20% of patients with moderate to severe AD, while the frequency of agitation and aggression is around 30-45% in the same population. The emergence and worsening of these symptoms correlate with the accelerated cognitive and functional decline of patients, resulting in early transfer to institutional care, hospitalisation and early death.

Moreover, these symptoms represent an aspect of disease burden that is physically, emotionally, and economically challenging, imposing an excessive burden on caregivers and resulting in high direct costs to the healthcare system. The direct cost to healthcare systems increases with disease severity and patients with advanced AD demand disproportionate resources due to high rates of long-term nursing home placement and hospitalisation.

In the absence of a cure for AD, prevention of symptomatic worsening is a relevant and realistic treatment outcome. Stabilisation of AD symptoms is especially important in the moderate to severe stages of AD, where the rate of decline is most pronounced.

Current management of AD in the UK

Two classes of drugs with differing mechanisms of action are licensed for the treatment of AD:

- Acetyl cholinesterase inhibitors (AChEIs) for the treatment of mild and moderate AD (donepezil, galantamine, rivastigmine); and
- The N-methyl-D-aspartate receptor antagonist, memantine, for the treatment of moderate to severe AD.

The AChEIs represent the conventional pharmacological option for the management of patients with moderate AD in the UK. However, there is an identifiable proportion of AD patients for whom AChEIs are not appropriate, due to disease severity, intolerance, contraindications or patients who show insufficient response to AChEI treatment alone.

Memantine is a well tolerated and effective treatment alternative for moderate AD patients for whom AChEIs are not suitable. Memantine may be given as monotherapy or as adjunct in patients who show insufficient response to AChEIs alone. In addition, memantine is the only treatment licensed in the UK for the treatment of severe AD.

The antipsychotic medication risperidone is also indicated for the short-term treatment only (up to 6 weeks) of persistent aggression in patients with moderate to severe AD. However, evidence suggests that the potential benefit of antipsychotic use in patients with dementia is likely to be outweighed by the high risk of adverse events.

Clinical effectiveness

Data is presented in this submission to demonstrate the clinical and related treatment benefits of memantine in two patient groups:

- The general population of patients with moderate to severe AD; and
- A sub-group of moderate to severe AD patients presenting with agitation/aggression and/or psychotic symptoms (APS) at the start of treatment. Within the memantine target population, this sub-group has consistently been shown to differ from the remaining population in terms of patient characteristics (greater clinical decline), medical need (frequent misuse of antipsychotic drugs in AD) and higher economic burden.

The majority of the data presented in this submission were not available for the NICE Appraisal Committee to consider during the 2004 review (TA111) and are therefore presented here to NICE for the first time. Steps have also been taken to address concerns raised in the previous review by validating the definition and clinical plausibility of the sub-group of patients with APS.

A meta-analysis of the six pivotal randomised clinical trials (RCTs) was performed to investigate the clinical benefits of memantine in the general population of patients with moderate to severe AD. The results demonstrated that:

- There is a significant treatment effect in favour of memantine for all four key efficacy domains (cognitive, function, behaviour and global status) compared to no treatment, such that the deterioration of AD symptoms is attenuated over time.
- Memantine is as effective in patients with severe AD as it is in patients with moderate AD. Memantine demonstrates significant treatment benefits given either as monotherapy or adjunctive therapy with a stable dose of an AChEI. These treatment effects for memantine are consistent, regardless of history of past use of AChEIs.
- Memantine presents additional benefits in the general population by preventing the emergence of agitation/aggression and/or psychotic symptoms, which are known predictors of accelerated cognitive and functional decline, increased caregiver burden and early transfer to institutional care.
- A sub-group analysis in patients with APS demonstrated that, in addition to the treatment effects seen in the general population, memantine is associated with enhanced treatment benefits:
 - Control of APS in this population has been achieved after 12-weeks treatment.
 - The treatment effects on cognition and functioning were considerably higher in this sub-group than in all patients with moderate to severe AD, and there is some data to suggest that memantine is at least as effective as risperidone in the treatment of agitation and aggression.

Memantine is generally well tolerated, and in contrast to antipsychotics used in dementia, is not associated with an increased risk of cerebrovascular events, mortality and worsening cognition.

Evidence from real-life clinical settings has confirmed and extended the findings from clinical trials and indicates that memantine may control behavioural disturbance, reduce reliance on antipsychotic medication, lower rates of cognitive and functional decline, decrease caregiver burden and reduce the risk of institutionalisation with delayed admission. Memantine is well tolerated, with adverse event rates similar to those reported for placebo.

Cost Effectiveness

Lundbeck has addressed comments made during the course of TA111 to present an updated and robust health economic model, supported by a greater body of evidence than was available to inform the previous submission. The economic model evaluated the long-term health and economic impact of memantine in moderate to severe AD based on the concept of a need for full-time care (FTC). Patients requiring FTC have low cognitive and functional abilities, and therefore represent a major burden on carers and healthcare resources.

A cost-utility analysis was based on a Markov model simulating time to FTC in the two targeted populations (namely, the general population of patients with moderate to severe AD and the sub-group of patients with APS). Transition probabilities, resource use, utilities and mortality were obtained from the London and South-East Region (LASER) epidemiological study. Memantine efficacy was based on a meta-analysis of six large trials. Treatment with memantine, as monotherapy or in adjunct to AChEIs, was assessed in relation to patient management in practice for moderate to severe AD in the UK (i.e. treatment with an AChEI or no pharmacological treatment).

Over a 5-year time horizon, treatment with memantine in the general population of moderate to severe AD patients was associated with a delay to FTC (6 weeks) and an incremental improvement in QALYs gained (+0.031) for no additional cost (a cost saving of -£1,711). Greater benefits were observed in the sub-group of patients with APS: the time to FTC was prolonged by up to 11 weeks with incremental QALY gains of 0.069 and a cost saving of -£4,971. Memantine was cost-effective for both the general population and the APS sub-group across a wide range of assumptions.

Wider Implications

By 2015, it is estimated that 206,273 people in the UK will develop moderate to severe AD. Of these, it is expected that almost 134,000 patients could be eligible for treatment with memantine; this includes approximately 16,000 patients in the APS sub-group who could benefit from memantine to replace inappropriate use of antipsychotic medications. The net budget impact compared to no change in NICE current recommendations for the general moderate to severe population is estimated to be between £4.4-8.9 million per annum (total of £32.3 million over five years). Specifically targeting the incident APS sub-group would not put additional burden on NHS budgets. In this sub-group, memantine treatment would result in substantial resource savings associated with delayed institutionalisation, lower requirements for care, and less reliance on antipsychotic treatments with improved quality of life for patients and carers. Memantine therapy further supports NICE and wider societal objectives in promoting social values related to age, individual choice, stigma, equality and disability/quality of life. By not adopting memantine in the NHS for specific patient groups, this would deny these patients an effective alternative to inappropriate antipsychotic therapy.

Conclusions

Memantine offers clear benefits in cognition, function, behaviour and global status for moderate to severe AD patients and is cost-effective at current thresholds. Furthermore, sub-group analyses have demonstrated that memantine is beneficial in patients with agitation/aggression and/or psychotic symptoms who, despite normal accelerated decline and higher disease burden, may have the same progression as the overall population when treated with memantine. This results in a higher effect size and greater economic benefits for memantine versus standard care when used in this sub-group.

Given the current established treatment pathways for AD in the UK, the data suggest that memantine is clinically and cost-effective in the following patient populations:

- Moderate patients with APS;
- Moderate patients withdrawn from AChEIs;
- Moderate patients requiring adjunct treatment while on a stable dose of an AChEI; and
- Patients with severe AD.

Patients with moderate AD, who either require adjunct treatment or are withdrawn from or contraindicated for AChEIs, and patients with severe AD, have no other licensed treatment options. These patients represent those with the greatest unmet medical need, for which economic and societal considerations are most relevant.

2.0 BACKGROUND SECTION

KEY POINTS

- Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder. The advanced stages of AD are characterised by a rapid loss of cognitive function, decline in ability to perform activities of daily living, and emergence and worsening of psychotic symptoms and behavioural disturbances such as agitation and aggression.
- Agitation, aggression and psychotic symptoms are highly prevalent during moderate to severe AD. The emergence and worsening of these symptoms accelerate patients' cognitive and functional decline, imposing excessive burden on caregivers. This leads to cessation of informal care and consequential institutionalisation and hospitalisation.
- Not surprisingly, the direct cost to healthcare systems increases with the severity of the disease. Patients with advanced AD demand disproportionately larger resources of the healthcare system due to high rates of hospitalisation and long-term nursing home placement.
- In the absence of a cure for AD, prevention of symptomatic worsening is a relevant and realistic treatment outcome. Stabilisation of AD symptoms is especially important in the moderate to severe stages of AD, where the rate of decline is most pronounced.
- Treatment with acetyl cholinesterase inhibitors (AChEIs) is a conventional pharmacological management of patients with moderate AD in the UK. In addition, risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe AD. In practice, many antipsychotic drugs are given to AD patients despite a critical concern about using these medications in AD patients due to the elevated risk of serious and life-threatening adverse events.
- Memantine represents a well tolerated and effective treatment alternative to patients for whom AChEIs are not appropriate due to disease severity, intolerance or contraindications. Memantine can also be given as adjunct to an AChEI in patients who show insufficient response to an AChEI alone. Furthermore it may be a preferred treatment choice for patients with aggression/agitation and/or psychotic symptoms due to significantly greater overall benefit (i.e. cognition and function) than placebo and effective management of these symptoms.
- International clinical guidelines recommend memantine and it is widely used outside the UK.

2.1. Clinical Characteristics of Alzheimer's Disease (AD)

AD, the most common type of dementia, is a chronic progressive neurodegenerative disorder with an insidious onset. It is characterised by a progressive loss of cognitive and intellectual function, the ability to perform the activities of daily living as well as emergence of behavioural and psychological symptoms. The clinical spectrum of AD resides on a continuum making initial signs barely detectable and rates of decline vary widely. The progression of AD is conventionally divided into three stages: mild, moderate and severe, based on the domains of cognition, function, behaviour and global status.^{1, 2} The median survival period from the diagnosis of AD is approximately 6 years (range 1–16 years), with about one-third of the time being spent in the severe stage.³⁻⁵

The disease evolves on three core domains:

Cognitive impairment: Early, subtle symptoms of cognitive impairment, include memory loss, disorientation and confusion.² Such cognitive impairment dominates the early stage of AD. Progressively, patients develop marked impairments in expressive and receptive language/communication, in their ability to plan and organise activities, and in virtually all other aspects of cognition. Slowing of cognitive processing, attention, and fluctuating attention is common in patients with moderate to severe AD.⁶

Functional impairment: Functional impairment relates to instrumental activities of daily living such as managing finances, using the telephone, driving a car, taking medications, planning a meal, etc. In

addition, it can also be associated with loss of basic activities of daily living (self-maintenance skills) such as using the toilet, dressing, grooming, eating and walking. After the initial phase of progressive memory or cognitive deficits (MMSE score ≥ 20) the growing need for assistance with activities of daily living heralds the onset of the moderate stage of the disease. Typically, problems first appear in the conduct of instrumental activities of daily living and progress to inability to manage simpler basic tasks of daily living ultimately deteriorating to total dependence on carer.⁷ Dependent patients become oblivious of their surroundings and cannot live alone because they require help with eating, drinking, dressing, personal hygiene and toileting.

Behavioural and psychological symptoms: Patients with AD present with a wide range of behavioural and psychological symptoms (BPSD – Behavioural and Psychological Symptoms of Dementia) that evolve over time. The classification of BPSD is typically phenomenological and describes patients' mental state and problematic behaviours. BPSD tend to occur in clusters, however, within symptom clusters, various symptoms may overlap with one another:

- Mood disorders or 'affective symptoms', including depression/dysphoria, anxiety, apathy, elation/euphoria, disinhibition⁸
- Psychotic symptoms, including delusions and hallucinations,⁸ and misidentifications⁹
- Behavioural symptoms, including agitation/aggression and irritability, aberrant motor behaviour, night-time behaviour, appetite/eating changes,⁸ stereotypes,¹⁰ hyperorality and hypersexuality¹¹

BPSD can be present in all stages of AD, but usually worsens as AD progresses. BPSD exhibit chronicity and tend to be persistent over the long term, while individual symptoms may run an intermittent course. Severe symptoms are also found to be persistent over time.^{12, 13}

Notably, as the disease progresses mood disorders start to diminish, in contrast to psychotic and behavioural problems that increase in frequency and severity during moderate and severe stages.¹³⁻¹⁵ Psychosis and behavioural symptoms such as agitation and aggression are common in the moderate and severe stages of the disease, tend to be more persistent and recurrent,^{13, 16-20} and represent an aspect of disease burden that is physically, emotionally, and economically challenging.²¹ Furthermore, these symptoms correlate with accelerated cognitive and functional decline,^{5, 15, 16, 22-27} and early transfer to institutional care and early death,^{1, 28, 29} regardless of concomitant usage of psychotropic medication.^{26, 27}

2.2 Assessment Tools in AD

Determining the stage of AD in a given patient requires the assessment of multiple domains³⁰ to reflect the clinical characteristics of the disease:

Cognition: The mini-mental state examination (MMSE) evaluates cognitive impairment. Moderate to severe AD patients are defined as having an MMSE score below 20. Although the MMSE is useful in differentiating between patients with different cognitive abilities, it has been reported to exhibit both floor and ceiling effects that make it less sensitive than other instruments for detecting change in moderate to severe patients.³¹ Two additional scales have been developed to better capture characteristics of early and late stages of the disease. The Alzheimer's disease assessment scale (ADAS-cog) assesses cognitive abilities such as memory, language and attention. As with the MMSE, the ADAS-cog may be less relevant in patients with severely impaired cognitive ability.³² The Severe Impairment Battery (SIB)³² is usually used in patients with severe Alzheimer's disease.

Functioning: ADCS-ADL₁₉, and the ADCD-ADL₂₃ have been shown to be suitable measures of function, with the former more adapted for advanced stages of AD.^{33, 34}

Behavioural: The Neuropsychiatric Inventory (NPI) is a validated clinical instrument for evaluating psychopathology in dementia. It includes a wide range of symptoms from mood disorders that characterise the early phase of AD (e.g. apathy, elation) to psychotic/agitation symptoms that characterise the later phases of AD. The NPI total score reflects a sum of diverse behaviours and is therefore acknowledged as a rough guide of the behavioural disturbance of the patient. It is

recommended for evaluating effects of treatment intervention on each individual or cluster of NPI symptoms.^{15, 35, 36}

Global status: The Clinician Interview-Based Impression of Change with carers input (CIBC-Plus) measures the global health of the patient as perceived by the physician.^{37, 38} This scale presents the advantage of measuring drug benefit from the physician perspective.

2.3 Epidemiology

The global estimate of dementia in 2001 was 24.3 million people with 4.6 million new cases of dementia occurring every year.³⁹ Alzheimer's Disease International (ADI) predicts that over the next 20 years the number of people with dementia is expected to increase by 40 per cent in Europe within the ageing population.

2.3.1 Prevalence of Alzheimer's Disease in the UK

In the UK, the prevalence of dementia is estimated at 3.83% in people over 65.⁴⁰ There is a common problem of under-diagnosis of AD and total estimates of diagnosed and non-diagnosed patients combined are larger (Table 2.1). Prevalence is known to drastically increase with age.

Table 2.1. EURODEM prevalence rates of diagnosed and undiagnosed dementia in the UK by age⁴¹

Age group, years	30-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94
Male	0.16%	1.58%	2.17%	4.61%	5.04%	12.12%	18.45%	32.10%
Female	0.09%	0.47%	1.10%	3.86%	6.67%	13.50%	22.76%	32.35%

The incidence rate of AD in people over the age of 65 years has been estimated at 4.9 per 1000 patient years in the UK⁴² with women carrying a higher risk.⁴³ A study in the UK estimated that 550 new cases of AD could be expected each year in the 45-64 years age group.⁴⁴ A large proportion of patients are estimated to be in the moderate (31%) and severe (21%) stages of the disease.⁴⁵

2.3.2 Prevalence of Agitation, Aggression and Psychosis

The moderate to severe stages of AD are characterised by worsening of psychotic and behavioural symptoms, especially agitation, aggression and psychotic symptoms. Psychosis affects more than 20% of moderate to severe AD patients.^{46, 47} The frequency of delusions in AD is approximately 20%^{1, 11, 16, 48-52} and 10% due to hallucinations.^{11, 16, 50, 52} The frequency of agitation and aggression is around 30-45% in the same population.¹⁵ In line with this, 45% of the moderate to severe patients from the LASER-AD study presented with agitation, aggression or psychosis (Appendix M). An additional analysis of the GPRD database is currently underway to investigate trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease treated with AD drugs in the UK (data on file).

2.4 Burden of Disease

The rise in the number of people with dementia fuelled by increasing life expectancies in developed countries around the world is causing widespread concern. The total economic burden of dementia in Europe is estimated to be €55–€66 billion annually based on 2003 values.⁵³ In the UK, the estimated direct cost of AD is between £7.06 and £14.93 billion.⁵⁴ These estimates include informal care costs in addition to health care and home care services but do not include indirect costs caused by a loss of productivity.

Care provided by family and friends can determine whether older persons can remain longer at home. It has been estimated that persons with AD require an average of 70 hours of care per week, with 62 of those hours provided by the primary carer.⁵⁵ In the UK, it is estimated that 1,509 million hours of informal care are provided by carers and 34% of this care is from economically active individuals leading to a total annual cost of £12,383 million.⁴¹ This unpaid informal care does not impact direct costs to the healthcare

system. However, carers experience social, emotional, physical, financial and quality of life burdens and may incur opportunity costs. These burdens become more significant as the disease progresses.^{14, 56, 57}

Psychosis is a major clinical symptom associated with AD that is extremely difficult for carers and for the society at large.^{46, 48} Psychosis and disruptive behaviour are two major cost drivers in AD. The largest increases in resource use occur where delusions, hallucinations, agitation/aggression, anxiety, irritability/lability, and aberrant motor behaviour are present.⁵⁸ The emergence or increase in behavioural symptoms, especially agitation and aggression have been identified as the most troublesome for caregivers, leading to increased caregiver burden and earlier institutionalisation.^{1, 5, 14, 28, 46, 59-61}

The LASER-AD study^{12, 62} aimed to determine the persistence and change in severity of neuropsychiatric symptoms (NPS) over 6 months in participants with AD and the relationship to cost of care. The study observed that patients with at least one clinically significant neuropsychiatric symptom had higher costs of care than those without NPS. One-third of patients classified as non-dependent but with instrumental functional disability (ND-IFD) lived in an institution. Among patients classified as dependent, the proportion of patients who lived in an institution increased nearly two-thirds. Costs were significantly associated with the patient's level of disability, with dependent patients incurring the highest care costs over six months (£22,510 ± £24,570). Time spent by informal carers (for patients living in the community) was significantly associated with the patient's level of disability – with monthly informal care time of 523 hours ± 289 for dependent patients, 322 ± 290 for ND-IFD patients, and 222 ± 275 with non-dependent patients.

2.5 Current Disease Management

In the absence of a cure, prevention of further worsening of symptoms is a relevant and realistic treatment goal.^{63, 64} Postponing or stabilising decline in any of the key symptoms represents a meaningful benefit to both patients and their carers. Improvement of symptoms is desirable but is rarely achievable with symptomatic treatment available to date. It has been suggested that the primary goals for treating patients with AD should also include the enhancement of independence and the maintenance of quality of life for both patients and caregivers.^{14, 65}

Two classes of drugs with differing mechanisms of action are licensed for the treatment of AD:

- Acetyl cholinesterase inhibitors (AChEIs) for the treatment of mild and moderate AD (Donepezil, Galantamine, Rivastigmine Summary of Product Characteristics (SPCs))
- N-methyl-D-aspartate receptor antagonist, memantine, for the treatment of moderate to severe AD (Memantine SPC)

In addition, risperidone (an atypical antipsychotic) is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others (Risperidone SPC).

2.5.1 AChEIs

AChEIs are an important therapy option for patients with mild to moderate AD. It has been acknowledged that all medications in this class are efficacious for mild to moderate AD with overall benefits for stabilising or slowing decline in cognition, function, behaviour and clinical global change.^{66, 67} The evidence of the benefit on behavioural disturbance is more limited, and benefits seem to be more pronounced on affective symptoms appearing early in the disease like depression, anxiety and apathy.^{68, 69} A prospective study with clinically significant agitation at baseline demonstrated no significant benefit of donepezil on agitation.⁷⁰

All AChEIs have a similar profile of contraindications and warnings, related to their cholinomimetic mechanism of action. Consequently, AD patients with cardiovascular conditions including sick sinus syndrome, sino-atrial or atrio-ventricular block, myocardial infarction, unstable angina, congestive heart failure, asthma, obstructive pulmonary disease, or those at risk of peptic ulcers are not suitable candidates for receiving AChEI therapy. The frequency of adverse events is high, especially in relation to the gastrointestinal system.⁶⁷ Nearly one-third of patients receiving AChEIs discontinue treatment on

account of adverse events. Cohort studies show significantly increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia associated with the use of cholinesterase inhibitors.⁷¹ In addition, many AD patients are not suitable for AChEI therapy because of the higher incidence of adverse events and contraindications.

2.5.2 Memantine

Memantine is a voltage-dependent, moderate-affinity, uncompetitive NMDA antagonist. Memantine blocks the effects of tonic pathologically elevated levels of glutamate that may lead to neuronal dysfunction. For more information about the mode of action of the medication and its pharmacological profile please refer to Appendix A. As will be presented in section 3 on clinical efficacy, memantine has shown statistically significant benefits on the four main domains of AD (cognition, function, behaviour and clinical global change) in moderate to severe AD patients.⁷² Other independent analyses have supported these findings demonstrating that memantine provides symptomatic benefits in patients with moderate to severe AD⁷³ and prevents worsening.⁷⁴

2.5.3 Antipsychotic Use in AD Patients

Agitation, aggression or psychotic symptoms occur in the majority of people with dementia at some point in their illness. There have been a number of clinical trials of antipsychotics to treat these symptoms. A Cochrane review was performed in 2006 by Ballard et al.⁷⁵ to determine whether evidence supports the use of atypical antipsychotics for the treatment of agitation aggression, and psychotic symptoms in people with AD. Although some trials suggest that risperidone and olanzapine are useful in reducing aggression and risperidone reduces psychosis, both are associated with serious adverse events including worsening cognition, cerebrovascular events, extrapyramidal symptoms, Parkinsonism, sedation, oedema, upper respiratory tract infection, increased falls and increased mortality rates.⁷⁵⁻⁸² The review concluded that despite the modest efficacy, the significant increase in adverse events confirms that neither risperidone nor olanzapine should be used routinely to treat dementia patients with aggression or psychosis, unless there is severe distress or risk of physical harm to those living and working with the patient.⁷⁵ A meta-analysis of seventeen placebo controlled trials of atypical antipsychotics for the treatment of behavioural symptoms in people with dementia conducted by the Food and Drug Administration⁷⁸⁻⁸⁰ suggested a 1.6-1.7 fold increase in mortality in these studies. The deleterious effect is probably related to the common pharmacologic effects of all atypical antipsychotic medications. A peer-reviewed meta-analysis⁷⁶ of 15 placebo controlled studies (nine unpublished) found a similar increased risk in mortality (OR=1.54, 95% CI, 1.06, 2.23; P=0.01) with a risk difference of 0.01 (95% CI, 0.004, 0.02; P=0.01) for antipsychotics.

Although associated with serious adverse events, antipsychotics are frequently prescribed as first-line pharmacological treatment for neuropsychiatric symptoms in patients with dementia and for extended periods often without periodic review.⁷⁵ It should also be noted that although risperidone has a licensed indication for the short term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe AD, olanzapine is not licensed in the UK for use in these patients. A recent report has concluded that the high level of antipsychotic use in dementia patients indicates that the potential benefit in certain patients is likely to be outweighed by the high risk of adverse events.⁸³

2.5.4 Treatment Guidelines

Guidelines recognise that diagnosis of dementia and subtype of dementia need to be based on a wide array of indicators, including clinical history, examinations and appropriate investigations.⁵¹ The Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia⁴ also emphasised that the assessment of severe AD should include the assessment of behaviour, function, medical status, nutrition, safety and caregiver status, aside from measurement of cognitive function.

Once diagnosis of AD has been confirmed, all available treatment guidelines issued by the American Psychiatric Association,⁸⁴ the British Association for Psychopharmacology⁵¹ and the European Federation of Neurological Societies⁸⁵ recognise the role of AChEIs donepezil, rivastigmine, and galantamine in the treatment of mild to moderate AD as well as the role of memantine in the treatment of moderate to severe AD.

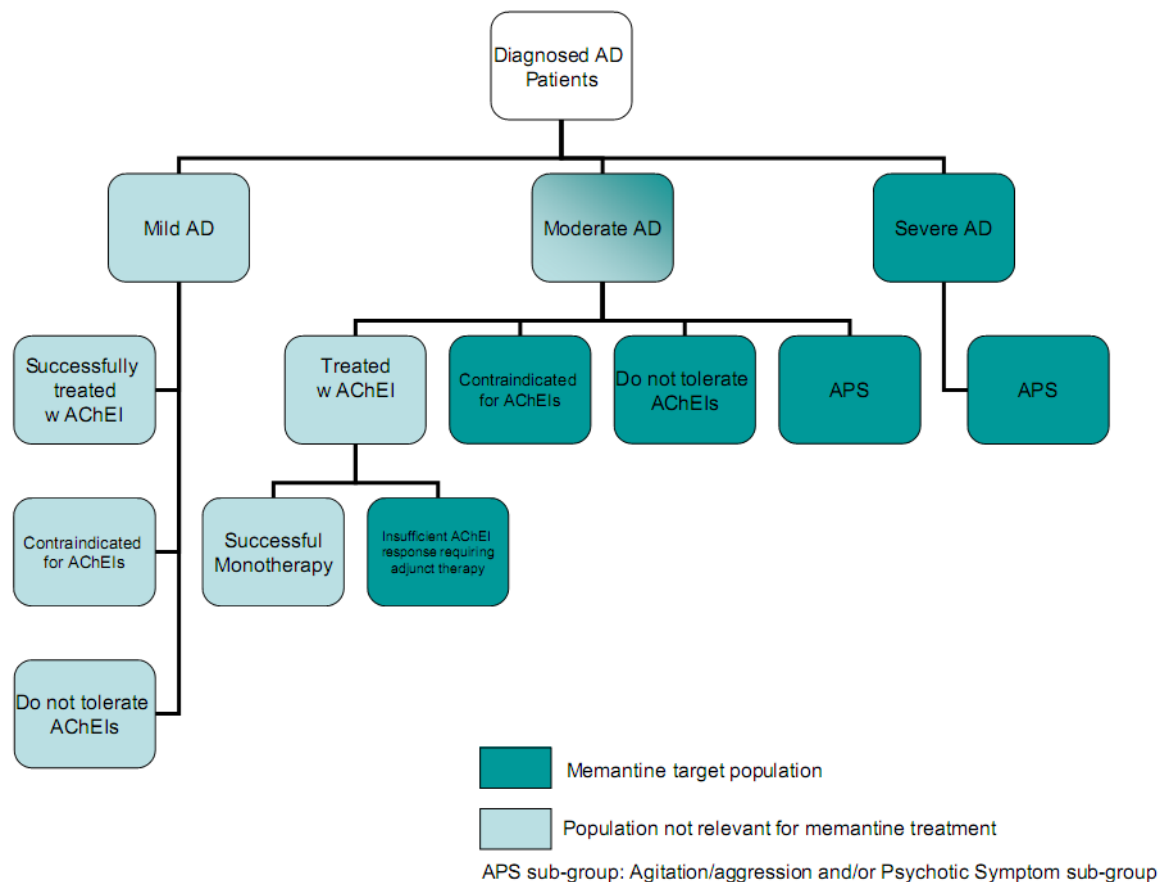
Recommendations for management of agitation, aggression, psychotic symptoms and other BPSD are more mixed compared to recommendations for cognitive deficits of AD. The APA guidelines⁸⁴ state that these patients may respond to environmental measures, including reassurance and redirection, or behavioural measures. Antipsychotics may also be used, the choice of treatment depending on the adverse effect profile and the characteristics of the individual patient. Anticonvulsants, lithium and beta-blockers have minimal evidence of efficacy in this population and have significant adverse effects; therefore they are generally not recommended. The antidepressant trazodone and selective serotonin reuptake inhibitors (SSRIs) are also not well studied for symptoms other than depression, but may be appropriate for nonpsychotic patients with agitation, especially for patients with mild agitation or prior sensitivity to antipsychotic medications. Both the BAP (2006)⁵¹ and the Canadian Consensus Conference (2008)⁴ state that many types of BPSD, including agitation, aggression and psychosis, have traditionally been treated with antipsychotic drugs, although the increased risk of cerebrovascular events and death need to be considered.

All pharmacologic approaches require careful monitoring and periodic reassessment to determine whether continued treatment is necessary.

2.6 Place of Memantine in the Treatment Programme for AD in the UK

Memantine was licensed in Europe in 2002 with the labelled indication of moderately severe to severe AD and a label extension for moderate to severe AD was made in Europe in 2005. Given the established treatment pathways for AD in the UK, memantine is best positioned to be used in the following patient populations (see Figure 2.1).

Figure 2.1. Memantine target population



Within the memantine target population, the sub-group with agitation/aggression and/or psychotic symptoms (APS) has been consistently shown to differ from the remaining population in terms of patient characteristics (greater clinical decline), medical need (frequent misuse of antipsychotic drugs in AD) and higher economic burden. Wilcock et al. 2008⁸⁶ have previously demonstrated that placebo-treated moderately severe to severe AD patients who score >0 on any of agitation/aggression, delusions or hallucinations at baseline using the NPI, experience more rapid disease progression in all AD domains when compared with patients without these symptoms at baseline; cognition - 87% more decline on SIB, function - 48% more decline on ADCS-ADL and global - 66% more decline on CIBIC-Plus.

At the request of NICE to identify sub-groups at the time of the previous submission (June 2005), Lundbeck defined a behaviourally disturbed sub-group (BDS) on the basis of the inclusion criteria identified and later published by Wilcock et al. (2008).⁸⁶ At the subsequent appeal hearing, the NICE team considered this definition too broad and suggested that it could therefore potentially include all patients with AD over time (transcripts from the appeal hearing 13th and 14th July 2006).

Though a definition of the BDS sub-group characterised by NPI scores >0 at baseline has been shown to contribute to accelerated decline in all AD domains, Lundbeck acknowledged the feedback from NICE at the appeal hearing to tighten this definition and lift the threshold for patient inclusion.⁸⁷ Therefore, the present submission considers the behavioural sub-group of interest as the moderate to severe AD patient cohort who scored ≥ 3 at baseline for any of agitation/aggression, delusions or hallucinations; hereafter more specifically termed the agitation/aggression and/or psychotic symptom (APS) sub-group.

This tightened definition has gained the support of a number of clinical experts in AD in the UK and is further supported by a consensus statement, referenced with this submission (Appendix B). It is also noteworthy that the APS sub-group, as currently defined, considers agitation/aggression and the psychotic symptoms (delusions and hallucinations) in the same manner previously adopted by studies that have examined the efficacy and safety of antipsychotic medication for patients with AD.⁸⁸

2.7 Description of the Decision Problem

Patients with mild to moderate AD have a clear treatment choice of several AChEIs. However there is a sizeable proportion of AD patients for whom AChEIs are not appropriate due to disease severity, intolerance contraindications, or patients who show insufficient response to AChEI treatment alone.

Moderate to severe AD patients, especially those with APS, represent the largest burden to the healthcare system, to family members, and to full-time care providers and society. Any clinical benefit of treatment in this population will allow patients to remain independent for a longer period, thereby reducing the burden on carers, and placing a smaller demand on the resources of both formal and informal care facilities. This is increasingly important as the number of AD patients is predicted to rise in line with an aging UK population.

Memantine offers clear benefits in cognition, function, behaviour and global impression for the moderate to severe population.⁷² In addition, sub-group analysis has shown that memantine is particularly beneficial in the patients with APS who despite natural accelerated decline and higher burden will have the same progression as the overall moderate to severe population when treated with memantine. This results in a larger effect size (i.e. a greater treatment benefit) and higher economic benefits for memantine versus standard care when treating this sub-group.

Considering the absence of therapy options in patients with the largest unmet need, the high disease burden, and also the potential of memantine to reduce the need of costly FTC and reduce carer burden, there is a clear benefit for the inclusion of memantine in NICE recommendations.

Based on the issues outlined above, the purpose of this submission is to present a complete set of evidence demonstrating clinical and cost effectiveness evidence of memantine, as well as the social priorities that should be considered in evaluating memantine's place in the management of AD in the UK. These arguments will be presented for the overall moderate to severe AD population as well as for the APS sub-group.

3.0 CLINICAL EFFECTIVENESS OF MEMANTINE

KEY POINTS

The combined evidence from the controlled trials evidence base has proved the benefits of memantine in patients with moderate to severe AD:

- Memantine attenuates the deterioration of AD symptoms over time with a significant effect on all efficacy domains, i.e. cognition, function, behaviour and global status. It is noteworthy that:
 - Memantine is as effective in patients with severe AD as it is in patients with moderate AD.
 - Memantine has been shown to have significant benefits when given as adjunct with a stable dose of an AChEI.
 - Treatment effects are consistent, regardless of history of past use of AChEIs.
- Memantine presents additional benefits by preventing the emergence of agitation/aggression and/or psychotic symptoms, which are known predictors of accelerated cognitive and functional decline, increased caregiver burden and early transfer to institutional care.
- A sub-group analysis in patients with agitation/aggression and/or psychotic symptoms has revealed that memantine is associated with enhanced treatment benefits in this clinically and economically challenging population.
 - The treatment effects on all outcomes were numerically higher in this sub-group relative to that in the remaining patients with moderate to severe AD.
 - Significant treatment advantage for memantine over placebo for all outcomes has been shown in this population after 12-weeks treatment.
 - An indirect comparison suggests that memantine is at least as effective as risperidone in the treatment of agitation and aggression, yet with a significantly better adverse event profile.

Evidence from real-life clinical settings has confirmed and extended the findings from clinical trials:

- Memantine is associated with lower rates of cognitive and functional decline and decreased caregiver burden.
- Memantine was shown to successfully control behavioural disturbances and reduce the use of antipsychotic medications
- Adjunctive therapy with memantine and AChEI was shown to reduce risk of institutionalisation and delay admission.

Memantine is well tolerated, with AE rates similar to those reported for placebo.

3.1 Memantine in Moderate to Severe AD

3.1.1 Methods

3.1.1.1 *Meta-analysis of Clinical Evidence on Memantine from RCT Environment*

A meta-analysis of the pivotal clinical trials has been performed to investigate and conclude on the clinical benefits of memantine in moderate to severe AD. The trials selected for the analysis were in accordance with the standards for the trial design in AD.⁸⁹ The inclusion criteria were:

- Use of memantine 20 mg/day over 24 weeks and longer in randomised double-blind placebo-controlled trials
- Availability of the assessments at the end of study and/or 24 weeks for four AD domains using standard recognised scales:

- Cognition (ADAS-cog or SIB)
- Disability (ADCS-ADL₁₉ or ADCS-ADL₂₃)
- Global health state (CIBIC-Plus or ADCS-CGI-C)
- Behaviour (NPI or NPI-NH)
- To enable analyses in an APS, availability of the assessments at the end of 12 weeks, and access to patient-level data for sub-group analyses was also required.

Six out of 32 clinical trials satisfied these criteria (see Appendix C for rationale by trial) and comprised the basis for the main analysis. Three of these trials were conducted in patients with moderately severe to severe disease (MMSE scores ≤ 14):

- MRZ 90001-9605/1⁹⁰
- Forest MEM-MD-01⁹¹
- Forest MEM-MD-02⁹²

The other three trials were performed in patients with mild to moderate disease (MMSE scores > 10). These studies lend support to the extension of the indication to include moderate AD:

- Lundbeck 99679⁹³
- Forest MEM-MD-10⁹⁴
- Forest MEM-MD-12⁹⁵

As none of the separate clinical trials is exactly representative of the population in which memantine is approved (moderate to severe AD, MMSE < 20), the data from all RCTs were pooled, excluding the patients with mild AD to enable evaluation of the efficacy of memantine within the marketing authorisation. In addition, three other trials (Asubio IE-2101, Forest MEM-MD-22, and Lundbeck 10112) were selected for sensitivity analyses, as these trials contained some supplementary information on the efficacy of memantine.

The details of the included and excluded trials and the methodological details of the performed analyses are presented in Appendices C, D and F.

3.1.1.2 Analyses of Homogeneity of Treatment Effect by Patient Characteristics

Notably the patient population in the memantine trials had distinct clinical profiles, e.g. symptom severity, history of AChEI treatment, presence of a background AD medication. Two of the pivotal trials, MEM-MD-02 and MEM-MD-12, evaluated efficacy of memantine as add-on therapy in patients on a stable dose of AChEIs. In the remaining four trials, memantine was given as a monotherapy. In these trials patients were not permitted to use AChEIs during the study; however, the patient population comprised both patients with a previous history of AChEI treatment and patients who were naïve to the AD medication.

Such diversity of the patient population is deemed to fairly reflect the real-life management of patients with advanced disease. Indeed, the well-documented floor effect of the MMSE scale impedes the use of the scale in routine clinical practice to establish patient severity, as the scale is not sensitive to differentiating moderate and severe patients once the disease progresses to the advanced stages.³¹ As presented in the background section, other factors apart from AD severity play a role when making a decision on suitable treatment management of AD symptoms. One such factor is patient suitability for the treatment with an AChEI. Given the established clinical practice for moderate AD in England and Wales, the vast majority of patients would be exposed to treatment with an AChEI at some point in the course of their disease. For some patients, stabilisation on an AChEI treatment could be successful. However a proportion of patients will be withdrawn from, or not be suitable for, the AChEI treatment due to intolerance or contraindications or will show insufficient response to AChEIs.

It is imperative to investigate whether memantine offers comparable benefits to all patients regardless of their characteristics. To meet this objective, the interaction analysis was chosen to be the most appropriate statistical technique. In line with the proposed positioning of memantine in the treatment programme, the following three hypotheses were tested:

- Does severity of the disease alter the magnitude of memantine effect?
- Does history of past use of AChEI alter the magnitude of memantine effect?
- Does presence of a background treatment with AChEIs alter the magnitude of memantine effect?

The methodological details of the analyses performed are presented in Appendix D. It should also be noted that the results of such analyses allow assessment of the validity of pooling data across patient sub-groups to establish the efficacy of memantine in moderate to severe AD.

3.1.2 Results

3.1.2.1 Efficacy of Memantine on Standard AD Endpoints in Patients with Moderate to Severe AD

The efficacy of memantine was exhaustively assessed on global, cognitive, functional and behavioural domains as measured by CIBIC-plus, ADAS-cog, SIB, ADCS-ADL, and NPI scales. Of the 2311 enrolled patients, 1826 (959 on memantine and 867 on placebo) had baseline MMSE scores <20, and constituted the target population with moderate to severe AD. The mean patient age was 76 years, and there were no clinically relevant differences between treatment groups in baseline demographic characteristics.

A statistically significant treatment effect in favour of memantine was found with respect to all four key efficacy domains. Memantine was found to be effective in attenuating deterioration of cognition, function, behaviour and global status (Table 3.1) and no evidence of heterogeneity was found for the data analysed. This analysis was published by Winblad et al., 2007.⁷²

Table 3.1. Summary of efficacy of memantine on standard AD endpoints in patients with moderate to severe AD, intention-to-treat population, observed cases (OC) approach, 24/28 weeks

Efficacy domain	SMD* (95% CI)	p –value
Cognitive (ADAS-cog, SIB)	-0.26 (-0.37, -0.16)	p<0.0001
Functional (ADCS-ADL)	-0.18 (-0.28, -0.08)	p=0.0007
Global (CIBIC-plus)	-0.22 (-0.32, -0.11)	p<0.0001
Behavioural (NPI)	-0.12 (-0.22, -0.01)	P=0.03
* Standardised mean difference of a change from baseline between treatment and placebo. Negative values indicate smaller decline with memantine over placebo, i.e. favour treatment group.		

The meta-analysis of the nine memantine RCTs showed similar results to those in the main analysis. Inclusion of the additional trials (MD-22, Lu-10112 and IE-2101) had no influence on the results and all conclusions remained unchanged.

Forest plots describing the results in each domain by trial, Last Observation Carried Forward (LOCF) analyses and analyses of heterogeneity can be found in Appendices D and E.

3.1.2.2 Analyses of Homogeneity of Treatment Effect by Patient Sub-group

3.1.2.2.1 Effect of Severity

The analysis aimed to establish whether there is a significant difference in memantine efficacy between patients with moderate and severe AD. The analysis was performed on the three moderately severe to severe AD trials. The trials in mild to moderate AD were not suitable for the purpose of this analysis as they did not recruit patients with severe disease. Among the 983 patients with at least one post-baseline evaluation, 525 (53.4%, 250 receiving memantine and 275 receiving placebo) were moderate (MMSE 10-14) and 458 (46.6%, 245 receiving memantine and 213 receiving placebo) were severe (MMSE <10).

Memantine was significantly superior to placebo on all outcomes (OC and LOCF analyses) in both the severe and the moderate sub-groups. The interaction between treatment effect and baseline severity was never significant (only a trend on cognition in OC, that was not confirmed in LOCF), thereby indicating no evidence of a different efficacy of memantine between moderate and severe patients. Please see Appendix H for more details.⁵⁹

3.1.2.2.2 *Effect of Past Use of AChEI*

The analysis aimed to establish whether there is a significant difference in memantine efficacy between patients who were previously treated with AChEIs and patients who were naïve to any AD medication. The analysis was performed on the four trials, where memantine was given as monotherapy. The two adjunct trials were not suitable for the purpose of this analysis. Of the 1096 patients available for the analysis (589 receiving memantine and 507 receiving placebo), 170 (15.5%) were previously treated with an AChEI. 60 (11.8%) in the placebo arm and 110 (18.7%) in the memantine arm.

Memantine was significantly superior to placebo on all outcomes for the population of naïve patients, both in OC and LOCF analyses. The interaction between treatment effect and history of AChEI use was not significant (all p-values above 0.6), thereby indicating no evidence of differing efficacy of memantine between naïve and previously treated patients. Please see Appendix E for more details.

3.1.2.2.3 *Effect of Concurrent Treatment with AChEI*

The analysis aimed to establish whether there is a significant difference in memantine efficacy between patients who were on stable dose with AChEIs and patients who were on no background pharmacological treatment. The analysis was performed on all six trials, comparing memantine efficacy when administered as a monotherapy or in adjunct to AChEIs. Of the 1788 patients (938 on memantine and 850 on placebo), 589 received memantine as a monotherapy and 349 in adjunct to AChEI.

Memantine was significantly superior to placebo on most outcomes, both as adjunct therapy and monotherapy. Other outcomes, namely function in adjunct (p=0.0551 in OC and p=0.0600 in LOCF) and global health state in adjunct for the LOCF analysis (p=0.0666), were close to significance level, despite lower sample size compared with base case analyses. The interaction between treatment effect and presence of background treatment was never significant. Please see Appendix E for more details.

3.1.2.2.4 *Conclusion*

Treatment with memantine, administered either as a monotherapy or as adjunct to AChEI, has demonstrated significant benefits on all core AD domains in moderate and severe AD. There was no evidence of superiority of a treatment effect in any of the analysed patient sub-groups, i.e. treatment effects were consistent regardless of the severity of AD symptoms, history of AChEI medication or concurrent treatment with AChEIs.

The results of the analyses indicate that memantine is an effective treatment alternative for:

- Moderate AD patients withdrawn from AChEIs;
- Moderate patients not previously treated with AChEIs;
- Moderate patients requiring adjunct treatment while on stable dose with AChEIs; and
- Patients with severe AD.

3.1.3 Clinical Relevance of Efficacy of Memantine in Moderate to Severe AD

This section contextualises the clinical relevance of the treatment effect of memantine by presenting the additional analyses performed on the data from memantine clinical trials.

3.1.3.1 *Memantine Prevents Deterioration*

In the absence of a cure, prevention of further worsening of symptoms is a relevant and realistic treatment goal.^{63, 64} Postponing or slowing decline in any of the key symptoms represents a potentially meaningful benefit to both patients and their carers.

The EMA guidelines⁸⁹ consider stabilisation of the triple response measure to correspond most closely to the responder definition introduced by the guidelines for trials in AD. In order to assess whether memantine prevents the worsening of AD in patients with moderate to severe disease, a triple responder analysis was performed comparing patients whose condition simultaneously worsened across global, cognitive, and functional domains during 6-month treatment. Two definitions were investigated:⁷²

- Marked Clinical Worsening – a decline of ≥ 4 points on the ADAS-cog or ≥ 5 points on the SIB and a decline on the CIBIC-plus and a decline on the ADCS-ADL
- Any Clinical Worsening – any decline on the ADAS-cog or on the SIB and any decline on the CIBIC-plus and any decline on the ADCS-ADL

The analysis was performed on the six pivotal trials that comprised the basis for the main meta-analysis on efficacy of memantine. The patient baseline demographics, characteristics and efficacy scores are shown in Appendices D and F. There were no clinically relevant differences between treatment groups.

The results of the triple responder analysis showed that almost twice as many placebo-treated patients had marked clinical worsening compared to memantine-treated patients (21% vs. 11%; $p < 0.001$, Table 3.2). Significantly more placebo-treated patients had any clinical worsening compared to memantine-treated patients (28% vs. 18%; $p < 0.001$ OC, Table 3.2) over the course of the 6-month treatment. The LOCF analyses showed similar results as those using OC, and the treatment differences in both evaluations were statistically significant. Marked clinical worsening was determined both for the patients in the monotherapy studies and for those in the studies in which memantine was given with a stable dose of an AChEI. There were no relevant differences in the effect of memantine in reducing clinical worsening when memantine was given alone or as adjunct with an AChEI. In both groups, occurrence of marked clinical worsening was halved by memantine compared to placebo.

Table 3.2. Proportion of patients with any clinical worsening and marked clinical worsening, moderate to severe AD population, OC, week 24/28

Response criterion	Memantine % (n_w / N)	Placebo % (n_w / N)	Difference %	P-value ^c
Marked Clinical Worsening	10.8% (86/ 797)	21.1% (143/ 678)	10.3%	<0.0001
Any Clinical Worsening	17.8% (142/ 797)	28.3% (192/ 678)	10.5%	<0.0001

n_w – number of patients showing worsening of symptoms; N – total number of patients in the group

^c – 2-sided Fisher's exact test.

The methodological details of the analyses performed and detailed results including LOCF analysis are presented in Appendix G.⁷⁴

3.1.3.2 Memantine controls behavioural symptoms in patients with moderate to severe AD

Optimising the management of patients with AD involves controlling existing behavioural changes as well as reducing the emergence of new symptoms. Effective management of agitation/aggression and/or psychotic symptoms is of particular importance as these symptoms correlate with accelerated cognitive and functional decline,^{23, 26, 27} and early transfer to institutional care,²⁸ independent of concomitant psychotropic medication usage.^{26, 27}

The focus of this analysis was an evaluation of the specific effects of memantine on behavioural disturbances by analysing the sub-domains of the NPI scale. In addition, the impact of treatment relative to the presence or absence of symptoms (NPI single items) at baseline was also assessed. To meet the objective of the analyses, the patient group was not specifically selected for having behavioural disturbances. The analysis was performed on the six pivotal trials that comprised the basis for the main meta-analysis on efficacy of memantine. The patient baseline demographics, characteristics and efficacy scores are shown in Appendix H.

The analysis showed that memantine-treated patients with moderate to severe AD had statistically significant benefits compared with placebo-treated patients, on the NPI total score, indicative of a benefit

of memantine on behavioural symptoms. Significant effects were seen as early as week 12. This observation was reinforced by specific analysis of NPI single items, which showed statistically significant differences in favour of memantine for the individual symptoms delusions, hallucinations, agitation/aggression and irritability/lability. For patients with behavioural symptoms at baseline, memantine was especially effective in improving present symptoms of delusions, agitation/aggression and disinhibition during the 6 months of treatment. In the subset of patients who were asymptomatic for the individual NPI items at baseline, significantly more memantine-treated patients than placebo-treated patients remained asymptomatic at week 12 in the items agitation/aggression, delusions and disinhibition. At week 24/28, significantly more memantine-treated patients than placebo-treated patients remained asymptomatic in the items agitation/aggression, irritability/lability and night-time behaviour.

The methodological details of the performed analyses, the detailed results including LOCF analysis are presented in Appendix H.⁵⁹

3.1.3.3 *Memantine has Beneficial Effects on Individual Clusters of Cognitive Domain in Patients with Moderate to Severe AD*

In moderate to severe AD, cognitive functions rapidly deteriorate resulting in functional impairment.⁷² It is equally important to understand which cognitive functions improve or stabilise under the treatment, thus contributing to the overall improvement of patient cognition measured by a total score.

This analysis focused on the three crucial domains of cognition, memory, language and praxis. Memory impairment is usually the first sign of the disease,⁹⁶ progressing to a pronounced amnesic syndrome in the moderate to severe stages, and heavily affecting patients' ability to perform activities of daily living.² The language scores address communication problems, which frequently present as word-finding difficulties. The pursuing disintegration of language skills in the later stages lead to increasing isolation by reducing patients' ability to interact and communicate. Similarly, items in the praxis cluster relate to patients' ability to deal with everyday activities. Consequently, any improvement or prevention of worsening in these functions is relevant treatment outcomes in patients with moderate to severe AD.

For the purposes of this analysis, ADAS-cog and SIB scores from all six studies were pooled and combined into three clusters representing language, memory and praxis. The responder analyses were performed on the Intent-To-Treat (ITT) population, using three different cut-offs any improvement, no change or any improvement and any worsening.

For the SIB scale, any improvement was defined as change from baseline >0 , no change or any improvement as change from baseline ≥ 0 , and any worsening as change from baseline <0 . For the ADAS-cog scale, any improvement was defined as change from baseline <0 , no change or any improvement as change from baseline ≥ 0 , and any worsening as change from baseline >0 . "Any worsening" and "no change or any improvement" were complementary categories, the "no change or any improvement" cut-off overlaps with the any improvement" cut-off.

The results of the responder analyses showed that a significantly higher proportion of memantine-treated patients had improvement on language, memory, and praxis scores compared with placebo-treated patients at week 12 and 24 (OC). Similarly, at both week 12 and week 24, a statistically significantly higher proportion of memantine-treated patients showed no change or any improvement than placebo-treated patients for each of the three clusters - memory, language and praxis. A reverse picture emerged in the analysis of worsening patients, favouring memantine at both weeks 12 and 24; a statistically significantly lower proportion of memantine-treated patients showed any worsening on either language, memory, or praxis compared with placebo. These results demonstrate that as a group patients treated with memantine perform better in these functions compared to non-treated patients.

The methodological details of the performed analyses, the detailed results are presented in Appendix I.⁹⁷

3.1.3.4 *Effect Size of Pharmacological Therapies for AD*

Several methods exist to facilitate judgment on clinical relevance of the observed treatment effects. Cohen's d approach, i.e. calculation of standardised mean difference (SMD), is the most commonly applied. SMD is particularly useful when there is a need to compare results across treatments. Also, it is

often used to enable meta-analysis of data obtained with different assessment scales provided that they measure the same outcome.

Judgment on clinical relevance of treatment effects based on effect size should always be considered within the context of the specific disease area. Within AD effect sizes across interventions are generally low. For example, an analysis of functional outcomes of pharmacological therapies in AD reports a standardised effect size of 0.1 to 0.4, but does highlight the consistent benefit of these treatments compared to placebo.⁹⁸ Given the severity and burden of AD, these effects represent important and relevant benefits to patients and their caregivers. Decision-makers should be aware of limitations of using such statistical measures in isolation of clinical expertise.⁹⁹

Despite this, a comparative analysis based on effect size could be a useful guide on achievable treatment targets in AD. We performed an indirect comparison of effect size of memantine and AChEIs in cognition, functioning, global and behavioural domains. In complementary analysis, an indirect comparison on safety outcomes was also carried out. The literature search was performed to identify all six-month double blind placebo-controlled randomised clinical trials of memantine, donepezil, galantamine and rivastigmine in AD. As the data available in the public domain was rarely presented by AD severity, the patient population in this analysis comprised patients with mild, moderate and severe AD, including patients treated with AChEI outside their licensed indication (severe AD). However, for memantine only data from moderate to severe patients (MMSE \leq 19) were used.

The comparison found memantine largely comparable in efficacy and superior in safety. The principal analyses on efficacy concluded to the non-inferiority of memantine compared to AChEIs on disability and behaviour. A consistent trend with borderline significant results towards non-inferiority of memantine compared with AChEIs on the global domain was also observed in all analyses. Numerically, memantine and AChEIs had similar efficacy on these three domains. Indirect comparisons performed on cognition were non conclusive. The results of the indirect comparison analysis were in accord with a recent small head-to-head trial between memantine and donepezil that showed no difference between the treatment arms on cognition and functioning.¹⁰⁰

Indirect comparison on safety revealed that adverse events were twice as likely to occur in AChEI-treated patients compared with memantine-treated patients. No significant difference in terms of serious adverse events was observed between memantine and AChEIs. Numerically, serious adverse events were similar between both treatment classes. A borderline difference was observed on dropouts due to adverse events, with AChEI-treated patients almost twice as likely to discontinue treatment due to adverse events compared with memantine-treated patients.

There are a number of factors that hinder the drawing of definite conclusions from such a comparison. The two classes of medications are indicated in distinct patient groups. Despite an overlapping indication in moderate AD, memantine is not directly positioned as a substitution for AChEIs but instead as an adjunct therapy in the treatment pathway. Furthermore, there are no major direct comparison studies in the indication for which both classes of drug have marketing authorisation, i.e. moderate AD. The analysis has a recognised limitation, i.e. it includes patient populations of any severity from AChEI trials as per data reported in the publications.

The methodological details of the performed analyses and detailed results are presented in Appendix J (commercial in confidence).

3.2 Memantine in Sub-group of Moderate to Severe AD Patients with Agitation/Aggression and/or Psychotic Symptoms (APS Sub-group)

3.2.1 Methods

3.2.1.1 Meta-analysis of Clinical Evidence on Memantine from RCT Environment

Wilcock et al. 2008⁸⁶ have previously demonstrated that placebo-treated moderately severe to severe AD patients who score >0 on any of agitation/aggression, delusions or hallucinations at baseline using the NPI, experience more rapid disease progression in all AD domains when compared with patients without

these symptoms at baseline; cognition - 87% more decline on SIB, function - 48% more decline on ADCS-ADL and global - 66% more decline on CIBIC-Plus.

At the request of NICE to identify sub-groups at the time of the previous submission (June 2005), Lundbeck defined a behaviourally disturbed sub-group (BDS) on the basis of the inclusion criteria identified and later published by Wilcock et al. (2008).⁸⁶ At the subsequent appeal hearing, the NICE team considered this definition too broad and suggested that it could therefore potentially include all patients with AD over time (transcripts from the appeal hearing 13th and 14th July 2006).

Though a definition of the APS sub-group characterised by NPI scores >0 at baseline has been clearly shown to contribute to accelerated decline in all AD domains, Lundbeck acknowledged the feedback from NICE at the appeal hearing to tighten this definition and lift the threshold for patient inclusion.⁸⁷ Therefore, the present submission considers the behavioural sub-group of interest as the moderate to severe AD patient cohort who score ≥ 3 at baseline for any of agitation/aggression, delusions or hallucinations; hereafter more specifically termed the agitation/aggression and/or psychotic symptom (APS) sub-group.

This tightened definition has gained the support of a number of clinical experts in AD in the UK and is further supported by a consensus statement, referenced with this submission (see appendix B). It is also noteworthy that the APS sub-group, as currently defined considers agitation/aggression and the psychotic symptoms (delusions and hallucinations) in the same manner previously adopted by studies that have examined the efficacy and safety of antipsychotic medication for patients with AD.⁸⁸

The choice of the threshold on NPI scale was tested in the sensitivity analysis, classifying patients in the APS sub-group based on presence of symptoms (NPI >0) and presence of more severe symptoms (NPI ≥ 4 , threshold based on data on file).

The same methodology was employed as for the previous analysis (section 3.1.1, Appendix D). In addition, the analyses were performed on the 12 week data to better capture acute treatment effects on psychotic symptoms and aggression/agitation. A shorter evaluation frame is necessitated by the intermittent course of individual BPSD symptoms.

3.2.1.2 *Meta-analysis of APS Sub-group*

The aim of this analysis was to characterise the baseline characteristics of the APS population (Table 3.3), establish efficacy in the APS and remaining population across all domains (Table 3.4) and to evaluate the decline on cognitive, functional and global domains in patients with and without APS using the ANCOVA models (Table 3.5). Twelve and 24 week data was analysed, applying OC and LOCF approaches. Further analysis details are presented in Appendix L.

3.2.2 Results

3.2.2.1 *Description of Patient Population in the APS Sub-group Analysis*

Overall, 31.3% of all patients included in the clinical trial cohort were defined as the APS sub-group at baseline, where this proportion within studies ranged from 22.3% to 44.8%. The proportion of APS patients increased with severity, especially at the lower end of the MMSE range, being roughly above 40% below a MMSE score of 5. Between MMSE scores of 5 and 17, this proportion remained between 20% and 40%. It is noteworthy that the proportion of APS patients remained relatively high at all severity stages in the population of interest.

Notably the APS sub-group was statistically different to the remaining population on all clinical assessments at baseline; insignificant differences were observed only in terms of demographic characteristics, age and gender (Table 3.3). Patients in the APS sub-group appeared significantly more affected compared with the remaining population for cognition, function, overall behaviour and all individual behavioural symptoms.

Table 3.3. Description of baseline characteristics per sub-group

Baseline characteristics	Overall population, moderate to severe AD (N=1826)	Patients APS (N=560)	Remaining patients (N=1166)	Difference between APS and Remaining Patients ⁴
Sociodemographics				
Age [mean ± SD]	76.1 ± 8.2	76.5 ± 7.9	75.9 ± 8.3	0.3663
Gender [n women (%)]	1168 (65.3%)	805 (65.6%)	363 (64.8%)	0.7628
Clinical evaluations				
MMSE [mean ± SD]	12.2 ± 4.2	11.3 ± 4.2	12.6 ± 4.2	<0.0001
ADAS-cog [mean ± SD] ¹	31.0 ± 10.0	33.7 ± 9.6	30.0 ± 9.9	<0.0001
SIB [mean ± SD] ²	75.0 ± 18.5	71.8 ± 20.4	76.7 ± 17.2	0.0006
Modified ADAS-cog [mean ± SD] ³	35.9 ± 11.3	38.7 ± 11.6	34.7 ± 10.9	<0.0001
ADCS-ADL ₂₃ [mean ± SD] ¹	52.1 ± 14.0	46.9 ± 14.4	54.0 ± 13.4	<0.0001
ADCS-ADL ₁₉ [mean ± SD] ²	32.9 ± 10.7	29.4 ± 10.3	34.7 ± 10.5	<0.0001
NPI total [mean ± SD]	15.4 ± 14.5	27.4 ± 16.4	9.7 ± 9.1	<0.0001
NPI delusion [mean ± SD]	1.1 ± 2.3	3.0 ± 3.2	0.2 ± 0.5	<0.0001
NPI hallucination [mean ± SD]	0.5 ± 1.5	1.3 ± 2.4	0.1 ± 0.3	<0.0001
NPI agitation [mean ± SD]	1.4 ± 2.3	3.7 ± 2.9	0.3 ± 0.6	<0.0001

1: only from Lu-99679, FRX-MD-10 and FRX-MD-12 clinical trials

2: only from MRZ-9605, FRX-MD-01 and FRX-MD-02 clinical trials

3: observed ADAS-cog for the Lu-99679, FRX-MD-10 and FRX-MD-12 clinical trials and estimated ADAS-cog for the MRZ-9605, FRX-MD-01 and FRX-MD-02 clinical trials

4: p-value related from APS from Wilcoxon-Mann-Whitney test (except for gender where Chi-square was used)

3.2.2.2 Efficacy of memantine on standard AD endpoints in APS sub-group

A summary of memantine efficacy results in the APS sub-group and remaining population at week 24/28 and week 12 is provided in Table 3.4. At 24/28 weeks, there was a significant treatment advantage for memantine over placebo for cognition, function, global status and additionally at 12 weeks for behaviour and NPI composite score on agitation/aggression, delusion and hallucination. All outcomes showed numerically higher effect sizes in the APS sub-group when compared with the remaining population, with the highest differences observed on cognition and function. Furthermore, treatment effects in the APS sub-group were also noted to be higher on all outcomes when compared to the overall moderate to severe population in Table 3.4.

Table 3.4. Summary of meta-analyses results in patients with APS and remaining patients

Based on OC Data	APS sub-group		Remaining population	
	SMD	P	SMD	P
Results at week 24/28				
Cognition	-0.35	0.0005	-0.23	0.0004
Functioning	-0.39	0.0000	-0.08	0.21
Global	-0.24	0.01	-0.20	0.002
Overall behaviour	-0.15	0.12	-0.07	0.24
NPI composite score on APS	-0.14	0.15	-0.12	0.06
Results at week 12				
Cognition	-0.36	0.0001	-0.29	0.0000
Functioning	-0.25	0.007	-0.02	0.79
Global	-0.22	0.02	-0.16	0.01
Overall behaviour	-0.28	0.002	-0.07	0.25
NPI composite score on APS	-0.25	0.006	-0.18	0.003

The large majority of significant results demonstrated in the meta-analyses were supported by significant results in individual studies (Appendix H), despite a reduced sample size (i.e., inclusion of a smaller sub-group and exclusion of mild patients from all trials in mild to moderate AD). This demonstrates that the significant benefit observed for memantine compared to placebo was not an artefact due to the effect of pooling.

Inclusion of the additional three clinical trials (IE2101, MD22, 10112) had no influence on the results and all conclusions remained unchanged. Furthermore, the impact of a choice of the threshold was tested. The meta-analyses were performed employing the thresholds of 0 and 4 on the same items of NPI scales and yielded similar results across all scenarios. Detailed presentation of the main findings and test for heterogeneity are presented in Appendix E.

3.2.2.3 Comparative Analyses of Clinical Evolution of APS Sub-group and Remaining Population

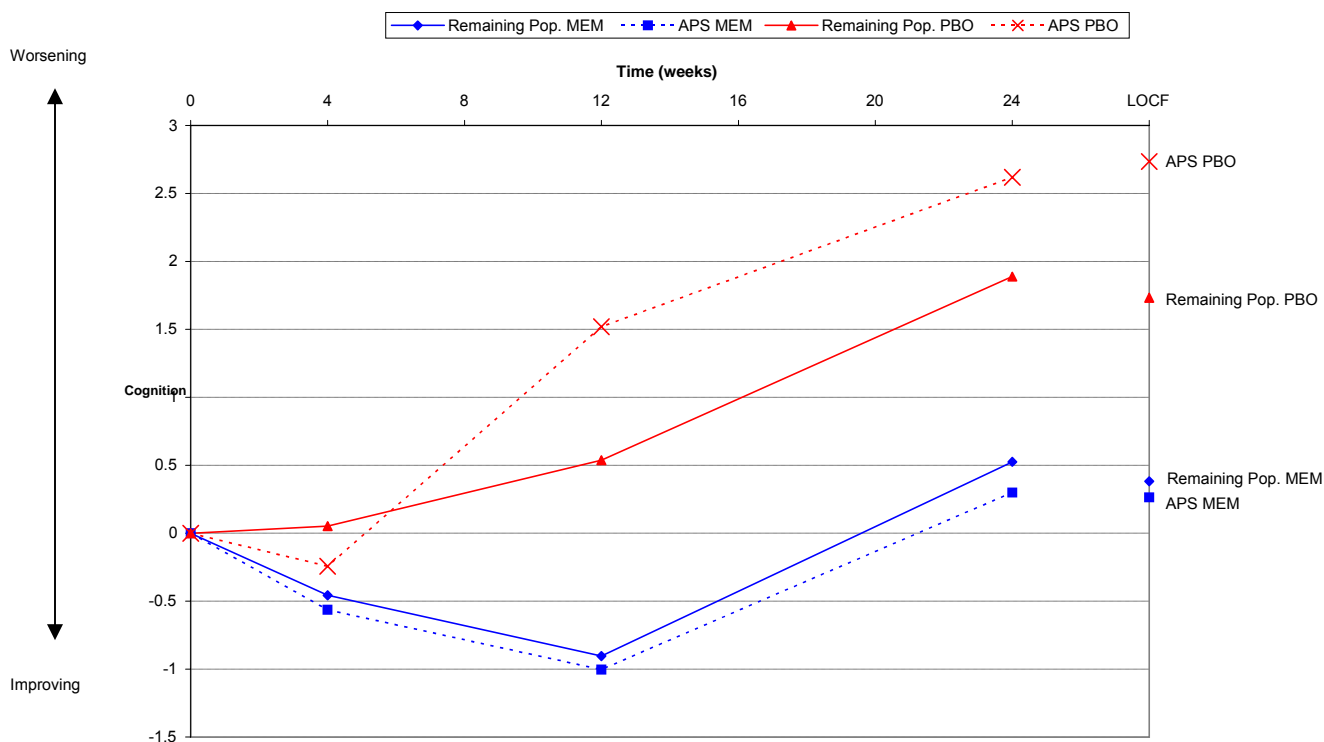
Differences in evolution of clinical assessments between the APS sub-group and the remaining population per treatment arm are summarised in Table 3.5. Placebo-treated patients in the APS sub-group showed a significantly faster decline compared with the remaining population on all domains: cognition (at week 12 in OC and endpoint in LOCF), function (all time points) and global status (all time points). Under memantine treatment, patients in the APS sub-group and the remaining population showed similar change on all domains (with the exception of global domain at week 24/28 in LOCF analysis). Notably, the differences between APS and remaining patients in the placebo group were always numerically higher than those in the memantine treatment group.

Table 3.5. Difference in evolution of clinical assessments between sub-groups per treatment

Scale	Analysis week	Difference APS sub-group vs. remaining population					
		Memantine			Placebo		
		Est.	SE	P	Est.	SE	P
Cognition (ADAS-cog)	12 (OC)	-0.10	0.42	0.8113	0.98	0.44	0.0249
	24/28 (OC)	-0.23	0.51	0.6565	0.73	0.55	0.1810
	24/28 (LOCF)	-0.12	0.46	0.7954	1.00	0.48	0.0358
Function (ADCS-ADL23)	12 (OC)	0.46	0.58	0.4207	-1.82	0.60	0.0023
	24/28 (OC)	0.09	0.72	0.9022	-3.22	0.77	0.0000
	24/28 (LOCF)	-0.55	0.67	0.4113	-2.67	0.70	0.0001
Global health state (CIBIC-plus)	12 (OC)	0.04	0.07	0.5581	0.19	0.07	0.0119
	24/28 (OC)	0.15	0.09	0.0819	0.24	0.09	0.0101
	24/28 (LOCF)	0.16	0.08	0.0367	0.22	0.08	0.0072

Clinical evolution of patients at all post baseline visits per treatment arm and sub-group are also plotted for illustration (Figure 3.1 for cognitive and Appendix L for function and global outcomes).

Collectively, these results support a faster decline in placebo-treated patients and a higher efficacy of memantine in the APS sub-group. Furthermore, the higher effect sizes for all outcomes are evident as early as week 12.

Figure 3.1. Evolution of cognition per treatment and patient profile

The current analyses demonstrate that patients with APS are a distinct sub-group from the remaining population in terms of clinical severity at baseline and in terms of rapid decline when left untreated. Memantine treatment confers significantly greater overall benefit than placebo in treatment of the APS sub-group, with the magnitude of effect being numerically greater than that observed in the remaining moderate to severe population. Furthermore, the higher effect sizes for all outcomes are evident as early as week 12, suggesting a more rapid onset of action of memantine within the APS sub-group.

3.3 Other Supporting Evidence

3.3.1 Indirect Comparison of Risperidone and Memantine

Inappropriate use of antipsychotics (including risperidone) in dementia patients has been shown to increase mortality.¹⁰¹ Given the proven clinical benefits of memantine in controlling psychotic behaviour in AD patients and in the absence of a direct comparison study, it is perceivable that an indirect comparison between the efficacy of antipsychotics and memantine is topical and relevant. Indirect comparison of risperidone and memantine in the APS sub-group indicates that memantine has at least similar efficacy on overall behavioural outcome and aggression sub-score when compared with risperidone. It should be noted that compared to risperidone memantine is effective on other core domains of AD. Drawing definite conclusions from this comparison is limited due to incomplete comparability of the patient populations in the analysis, e.g. difference in baseline severity and background medication for AD in memantine and risperidone trials. Please see Appendix K (Commercial in Confidence) for more details.

3.3.2 MAG-D Study

Memantine AGitation Dementia (MAG-D) is a prospective 12-week, randomised, placebo-controlled trial designed to assess the utility of memantine in a UK residential and inpatient setting for moderate to severe AD patients (MMSE ≤ 19) with clinically meaningful agitation that requires treatment.

The study is being conducted across 11 UK sites and inclusion criteria state the need for residential or inpatients aged no less than 55 with a history of ≥ 2 weeks of behavioural disturbance, a diagnosis of

moderate to severe AD and clinically significant agitation, as defined by the Cohen Mansfield Agitation Inventory (CMAI ≥ 45). A total of 154 patients have been recruited and the primary endpoint is defined as change in CMAI at week 6 – a difference of 5 points will favour memantine. Secondary endpoints recorded at weeks 6 and 12 will consider the NPI, CGI, SIB and Quality of Life measures. Final results are anticipated for late April / early May 2010, whereupon data will be made available to NICE for the review of TA111.

3.4 Real-life Effectiveness of Memantine in AD

Several manufacturers' post-marketing studies have been conducted in order to assess whether benefits of memantine demonstrated in the controlled environment of RCTs could be translated into the daily routine clinical practice. The effectiveness of memantine in traditional AD domains such as cognition, activities of daily living, behaviour disturbances and caregiver burden/distress, and the excellent tolerability/safety profile, of memantine have been confirmed and published.¹⁰²⁻¹¹¹

Moreover, it is important to emphasise that several independent international academic research teams also investigated real-life benefits of memantine and published strong supportive evidence for various outcomes. These included lowered antipsychotics consumption,¹¹² delayed time to institutionalisation,¹¹³ and long-term cognitive and function effectiveness,¹¹⁴ In total this makes up a weighted body of additional evidence for memantine coming from real-life settings. Further details can be found in Table 3.6.

Table 3.6. Summary of evidence from observational “real life” studies

Outcomes	Published real-life evidence	Messages
Cognition	^{102-107, 110}	Memantine monotherapy treatment is associated with an improvement of cognitive symptoms (as measured by MMSE)
	¹¹⁴	Memantine in adjunct to AChEI is associated with significantly lower rates of cognitive decline (as measured by Blessed Dementia Scale) compared with AChEI monotherapy or no treatment.
Function	^{102-107, 110}	Memantine monotherapy treatment is associated with an improvement of BADL/IADL (as measured by different scales -Katz, Lawton, FAST, FAQ, NOSGER)
	¹¹⁴	Memantine in adjunct to AChEI is associated with significantly lower rates of functional decline (as measured by Weintraub ADLs scale) compared with AChEI monotherapy or no treatment.
Behaviour	¹¹⁵	Memantine shows a significant benefit on psychiatric and behavioural symptoms in patients with moderate to severe AD in the NPI domains of delusions, agitation/aggression, and apathy/indifference.
	¹¹⁰	Improvement of behavioural symptoms (as measured by NPI-total score) after memantine treatment.
Responder analysis	¹¹⁶	Memantine produces both improvement and no deterioration of AD symptoms across multiple outcomes (cognition, function, behaviour & clinical impression of change),
Clinical Global Impression of Change	^{102, 104-109, 116}	Clinical global impression of change was assessed by the physicians as improved or stabilised for a high majority of patients treated by memantine.
Weight change	^{117, 118}	Memantine discontinuation is associated with a significant weight loss compared to continuous memantine treatment.
Use of antipsychotics	¹¹²	Memantine initiation stops the increasing trend in antipsychotic drug use among AD patients.
	¹¹⁵	Memantine treatment reduces the need for antipsychotic medication.
	^{117, 118}	Memantine discontinuation is associated with an increased utilisation of antipsychotics compared to continuous memantine treatment.
Caregiver	¹¹⁵	Memantine significantly decreases caregiver distress associated with

Outcomes	Published real-life evidence	Messages
burden / caregiver distress		patient delusions and apathy/indifference.
Resource Use	⁵⁸	Memantine's beneficial effects on specific behavioural symptoms, i.e. agitation/aggression, delusions, hallucinations, and irritability/lability, could translate into a reduction of the associated increased resource use.
Nursing home	¹¹³	Memantine in adjunct to AChEI delays nursing home admission compared with AChEI monotherapy or no treatment.
	^{117, 118}	Memantine discontinuation is associated with increased emergence or worsening of AD symptoms compared to continuous memantine treatment.
	^{108, 109}	Memantine treatment in Nursing home is associated with improvement of cognitive symptoms (as measured by MMSE), functional symptoms (as measured by FAST scale) and caregiver assessment (as measured by NOSGER scale).
Tolerability / Safety	^{102-106, 108-111, 116}	Memantine shows an excellent tolerability and safety profile, in monotherapy as well as in adjunct to AChEI.

FAST - Functional Assessment STaging scale; FAQ - Functional Assessment Questionnaire; NOSGER - Nurses' Observation Scale for Geriatric Patients

3.5 Safety

Overall, patient exposure in all completed and reported clinical trials so far since 2002 adds up to 4,799 patient years. The calculated exposure to memantine based on sales data exceeds 4 million patient years since launch. The latest Periodic Safety Update Report (PSUR 2009)¹¹⁹ included 295 case reports with mentions of convulsion, falls, occurrences of agitation, aggression, bradycardia, confusional state, pancreatitis, hallucinations, and hypertension, and 2 deaths were possibly related to memantine treatment. Taking patient exposure and occurrence of disease-related symptoms into account, there has been no increased frequency of listed adverse drug reactions.

Two safety reviews of memantine^{73, 120} and a meta-analysis on the tolerability and safety data from clinical trials¹²¹ concluded that memantine had a favourable tolerability profile when used as monotherapy or adjunct to other agents. The incidence of serious AEs was lower with memantine than with placebo,^{77, 120} and the AE profile for memantine in clinical was almost indistinguishable from that of placebo.¹²¹

Overall, the incidence of hallucination was 1.9% in the memantine group and 2.2% in the placebo group and the spontaneous reporting of hallucinations in post-marketing monitoring was low.¹²² In the placebo-controlled trials, the incidence of other psychotic-like treatment emergent adverse events (TEAEs), including delusions, delirium, manic reaction, psychosis, paranoid reaction, agitation, and paranoia was higher in the placebo group than in the memantine group. Only personality disorder (12 patients, 0.7% on memantine versus 5 patients, 0.3% on placebo) and depersonalisation (2 patients, 0.1% on memantine versus 0 on placebo) were more frequently reported with memantine than with placebo. Memantine has also been shown to be well tolerated when co-prescribed with other medications, which is a particular advantage for a drug prescribed for a target population in which polypharmacy is likely to be the norm.

Safety is a key factor in patients with AD because of the high level of comorbidity and exposure to other concomitant medications.⁷⁷ The limited contraindications, warnings and precautions associated with its use, combined with a low potential for drug-drug interactions make memantine a safe and simple treatment to administer to an elderly and frequently comorbid population. Memantine is a suitable choice for the treatment of an elderly patient population, with few, mild to moderate TEAEs and a low incidence of serious AEs comparable to placebo. On the other hand, the AChEIs are associated with more types of TEAEs because they have a high level of GI-related AEs, which are problematic for both carers and patients. The overall occurrence of TEAEs and withdrawals due to AEs are significantly higher with

AChEI treatment compared with placebo. Furthermore, due to their mechanism of action, there are serious concerns in using AChEIs in patients with comorbid cardiovascular and pulmonary conditions.⁷⁷ Memantine's safety profile also compares very positively with that of antipsychotics in this patient population. As discussed in section 2.5.3, the use of antipsychotics is associated with a significant increase in AEs and mortality in AD, therefore they are not suitable to treat dementia patients with agitation, aggression or psychosis.⁷⁵

3.6 Discussion

Moderate and severe AD represents the most difficult and distressing stages of the disease for patients, families, and carers. Patients with moderate to severe AD experience considerable cognitive, functional, and behavioural disability, and often undergo further disease progression related to an increase in behavioural symptoms such as agitation and psychosis.

In the management of AD patients, a realistic and clinically relevant treatment outcome is to slow the worsening of disease symptoms.⁶³ The clinical efficacy of memantine has been evaluated in 32 clinical trials. Six of these trials were suitable for inclusion in a meta-analysis to assess the use of memantine 20mg/day over 24 weeks or longer in a placebo-controlled trial, all of them allowing the assessment of treatment efficacy at the end of study for the four AD domains using standard recognised scales and allowing sub-population analyses at the same time. Although excluding a large number of trials ignores potentially relevant evidence on the efficacy of memantine, the excluded trials were conducted under different treatment protocols, used different outcomes or data was not available in sufficient detail. Therefore, their inclusion with the pooled evidence would have been invalid.

A significant treatment effect in favour of memantine was found with respect to all four key efficacy domains. Memantine was found to be effective in attenuating deterioration of cognition (SMD -0.26), function (SMD -0.18), behaviour (SMD -0.12) and global status (SMD -0.22).

The efficacy of memantine has also been assessed in the APS sub-group. The definition of the sub-group has been tightened in response to previous comments by NICE and in accordance with expert opinion. The current APS sub-group analyses demonstrate that patients with APS are observed to be more severe at baseline on cognition, function and behaviour and are found to undergo more rapid decline when left untreated. Memantine treatment confers significantly greater overall benefit than placebo when treating this challenging sub-group of patients with APS. The magnitude of effect is numerically greater than that observed in the remaining population. Furthermore, the higher effect sizes for all outcomes are evident as early as week 12, suggesting a more rapid onset of action of memantine within the APS sub-group.

Memantine was also found to be as effective in patients with severe AD as it was in patients with moderate AD. It has been shown to have significant benefits also when given adjunct with a stable dose of an AChEI, and treatment effects were consistent regardless of history of past use of AChEIs. In circumstances when AChEIs are not appropriate for moderate AD and for severe AD, memantine should be prescribed, barring intolerance or complications.¹²³

In both placebo-controlled trials and in real-life practice, memantine shows a favourable efficacy and safety profile. Memantine is well tolerated, with few drug-drug interactions. This is especially important as AD patients are often under polypharmacy and adverse events may cause further deterioration in functioning and exacerbate comorbid conditions.

4.0 COST EFFECTIVENESS

KEY POINTS

- The economic evaluation assessed the long-term health and economic impact of memantine in moderate to severe AD based on the need for Full Time Care (FTC).
- The need for FTC is a relevant outcome in moderate to severe AD. Patients requiring FTC present a major burden to carers and the healthcare system as AD is associated with significantly lower cognitive and functional abilities.
- The economic model was built on the data obtained from UK clinical practice. The predictive model presented here addresses some of the limitations of the original model by Stern et al., 1997¹²⁴ and its successors.^{125, 126} It allows for the inclusion of evidence on all measurable clinical manifestations of AD - cognition, functioning and behaviour - using standard AD scales.
- The cost-utility analysis was based on Markov cohort simulations over 5 years and performed in targeted populations, i.e. patients with moderate to severe AD and in a sub-group of patients with agitation/aggression and/or psychotic symptoms (APS).
- Treatment with memantine was assessed versus established patient management (treatment with an AChEI or no pharmacological treatment) for moderate to severe AD in the UK.
- The 5-year results of the economic evaluation show that memantine treatment for moderate to severe AD is associated with greater benefits with no additional costs to the healthcare system, as compared to standard care. The benefits of memantine are even greater in the sub-group of patients with APS.
 - Treatment with memantine in patients with moderate to severe AD was associated with a delay to FTC (6 weeks), an incremental improvement in QALY (+0.031), and no additional costs (-£1,711).
 - Even higher benefits were observed in the sub-group of patients with APS: the time to FTC was prolonged by up to 11 weeks, there was a QALY gain of 0.069, and a cost saving of -£4,971.
- In conclusion, memantine is cost-effective for both the general population and the APS sub-group across a wide range of assumptions and when key parameters are varied in sensitivity analyses.

4.1 Statement of Problem and Rationale for Modelling Approach

Statement of problem and perspective of cost-effectiveness analysis

The model estimates the cost-effectiveness of memantine plus usual care versus usual care alone in the UK for patients with moderate to severe AD, as well as for the APS sub-group, as this sub-group has higher medical needs and incurs higher use of resources. The perspective of the cost-effectiveness analysis is the NHS and PSS in England and Wales. Costs associated with patient care from the NHS and PSS are included in the analysis, together with all patient benefits.

Rationale for Modelling Approach

There is an extensive body of literature available evaluating the cost-effectiveness of AD therapies and the majority of these analyses have been undertaken using economic modelling. In a review of cost-effectiveness methodology in AD,¹²⁷ a critical analysis of how these models applied good practice guidance for health technology assessment (HTA) demonstrated several shortcomings. In particular, strong criticism was raised that nearly all models identified relied on cognitive scores alone to model disease progression. In addition, a general dearth of data for the modelling of treatment effects was noted. The economic model presented here addresses these criticisms by structuring the model around admission to FTC, applying an extensive body of clinical evidence from pivotal trials to model treatment

effects and applying UK specific epidemiological and cost data in order to most accurately present the cost-effectiveness of memantine from the perspective of NHS and PSS.

The economic model examined the entire population of moderate to severe AD patients. Based upon interaction tests between various sub-populations in this group (naïve patients vs. previously treated, moderate patients vs. severe patients, vs. adjunct therapy – see Appendix E for the complete analysis), it was concluded that the population was sufficiently homogeneous to be treated as a single population. In addition, the APS sub-group was considered based upon differential efficacy in this population and adjunct therapy was examined to explore possible differences from monotherapy.

4.2 Model Structure

This section presents a summary of the economic model structure, inputs and results. For detailed information, please refer to Appendix N.

4.2.1 Comparator

The comparator for memantine was standard care, which has been defined as any treatment received for AD. In the UK, for moderate patients, this could be AChEIs or no therapy and for severe patients, this would be no therapy. Standard care for patients not on an AChEI is considered to be receiving social support and assistance with day-to-day activities.

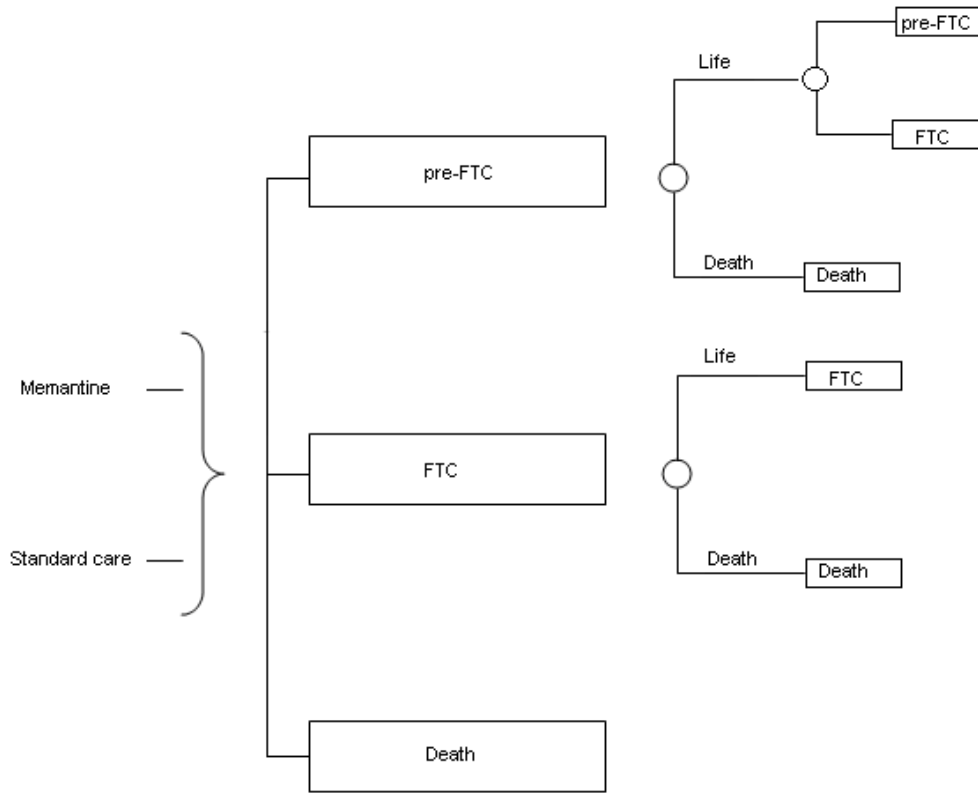
Considering established patient management in the UK for AD, memantine has been shown to be as effective in patients previously treated with AChEIs, treatment-naïve patients, and patients on a stable dose of AChEIs (see section 3.1.2.2). Therefore current standard care is a relevant comparator for the modelled populations (moderate to severe AD and the APS sub-group).

4.2.2 Model Structure

The need for FTC is a major burden of disease component because of the significantly low functional ability of FTC patients. These patients have a lower MMSE score, tend to be more frequently “severe”, have a higher ADAS-cog score and a lower SIB score. However, not all moderate to severe patients are in FTC and patients with moderate to severe AD who are not fully dependent on care givers are considered pre-FTC. FTC patients in particular have a poor HRQoL, especially in physical functioning and physical domains of the Health Status Questionnaire - 12 (HSQ - 12) and as measured by the Quality of Life in Alzheimer's Disease (QoL-AD) score.

Therefore, in the economic model the dominant defining event was the patient's need for FTC. A Markov cohort model was constructed to include the three stages of pre-FTC, FTC, and death in a patient's progression with AD. FTC was defined as a patient becoming either dependent or institutionalised. Death was included as a Markov stage because AD is associated with significant morbidity and an increased risk of mortality.¹²⁸ All patients were assumed to start in the pre-FTC state.

Transitions between the different health states of the model are presented in Figure 4.1.

Figure 4.1. Model schematic

4.2.3 Population

The modelled populations are consistent with the targeted population described in Section 2.6 and include patients suffering from moderate to severe AD who have no other licensed treatment options:

- Moderate AD patients withdrawn from AChEIs;
- Moderate patients contraindicated for AChEIs;
- Moderate patients requiring adjunct treatment while on stable dose with AChEIs; and
- Patients with severe AD.

The economic model was used to assess the cost-effectiveness of memantine in two patient populations:

- All targeted patients as above; and
- Sub-group with APS (see Section 2.6 for description of the definition).

4.2.4 Study Perspective

For patients suffering from AD, informal care represents a major component of care.¹²⁹ Therefore, both direct medical and non-medical costs considered under NHS and PSS were included. The burden of AD is high on the family and carers of patients; however the indirect costs and the quality of life effects on relatives or carers are not included due to the remit of this appraisal.

4.2.5 Time Horizon and Discounting

A time horizon of 5 years was chosen for the economic model because outcomes are dependent on a chronic progressive disease state with a low life-expectancy among patients with moderate to severe AD.

As in other FTC-based pharmacoeconomic models (e.g. Getsios et al., 2001¹²⁶), a length of one month was chosen for each Markov cycle, and repeated sixty times, yielding an analysis period of five years.

An annual discount rate of 3.5% was applied to both costs and health benefits occurring beyond the first year, reflecting the present recommendation from NICE.¹³⁰ Half-cycle correction was applied on all outcomes of the economic model (costs and health benefits) to account for transition between health states which may occur anytime within each cycle.

4.2.6 Duration of Treatment Administration and Treatment Effect

Memantine was assumed to be administered as long as patients remained in the pre-FTC state. However, the benefits of treatment were accounted for in the economic model only once. No additional benefit was assumed beyond 6 months, which is in accordance with the assumption in the AChEI model previously published by NICE:¹³¹ "eligible patients start treatment immediately and benefits from treatment are assumed to have an immediate effect, modifying patients' time-related risk of progression from pre-full-time care to the full-time care health state". This was implemented by deducting treatment effect on ADAS-cog, ADCS-ADL and NPI total from the patients' baseline data at the start of the economic model.

4.2.7 Implementation of the Model

The economic model has been implemented using TreeAge Pro 2009 Healthcare software from TreeAge Software, Inc Williamstown, MA 01267 USA. To assure quality control, the model was independently verified by a second independent modeller reconstructing the analysis based on the formal assumptions and inputs of the model. Results obtained were strictly identical in non-stochastic analyses and similar in stochastic analyses although programming was different.

4.3 Model Inputs

4.3.1 Main Effectiveness Data Sources

4.3.1.1 Real Life Data

The earlier stages of AD have been more studied and therefore the majority of the published data are related to this period instead of later stages of dementia. These findings could be explained by the lack of available treatments for more advanced stages of AD, before the introduction of memantine. Also, the focus of studies investigating the costs and burden of AD in the UK were on the impact on cognition only, rather than on functional disability.^{132, 133} Due to the shortcomings of published data, the LASER-AD study, a large longitudinal study of patients with AD and their caregivers, was performed in order to collect epidemiological, clinical and cost data in the UK. In this study 67% of patients were receiving AChEIs and the remaining 33% of patients received no therapy.⁶² See section 2.4 plus Appendix M for a description of the LASER-AD study.

The results of the LASER-AD study supported the relevance of loss of independence as a main cost driver⁶² and provided information regarding institutionalisation of patients, as well as validating the classification of dependency based on functional performance.

This model combined these criteria to obtain the efficacy outcome depending upon the need for full-time care. Of the 224 patients included in the LASER-AD study, 33 (14.7%) were dependent at baseline, 23 (10.3%) were institutionalised and 51 (22.8%) were both dependent and institutionalised. 117 remaining patients were analysed to derive the transition probabilities of going from pre-FTC to FTC in this model.

4.3.1.2 Randomised Clinical Trials

Clinical data for memantine treatment effects is based on a meta-analysis of moderate to severe AD from six pivotal clinical trials in the main analyses and from nine RCTs in a set of sensitivity analyses as described in Section 3.1 and Appendix F.

4.3.2 Transition Probabilities

The probability associated with various state-changes is assumed to depend only on the patient's health status at the beginning of the Markov cycle and on the adopted treatment strategy.

4.3.2.1 Pre-FTC to FTC transition probability

The log-log specification (cloglog), a discrete time representation of the Cox continuous time proportional hazards model, was used to estimate whether each patient at each time interval required FTC. Data from the LASER-AD study was applied to a cloglog model to derive the predictive equations to model the time to the FTC state in pre-FTC patients. The cloglog model was selected in order to accommodate time-dependent variables such as ADAS-Cog and ADCS-ADL.

Significant predictors of time to FTC for the analysis included ADAS-Cog total score,¹³⁴ baseline ADCS-ADL total score,³³ baseline NPI total score,¹³⁵ slope of decline in ADAS-cog total score, slope of decline in ADCS-ADL total score and time in months. The tabulation of the associated coefficients are found in Appendix N. The LASER-AD cohort was restricted to patients with moderate to severe AD (MMSE <20) who were in the pre-FTC stage to derive the values of the baseline parameters and slopes separately for each of the populations in the different scenarios.

In order to manage uncertainty around transition probabilities, normal distributions were selected for each component of the equation (baseline scores and slopes).

The transition probabilities for both memantine and standard care schemes used the same predictive equation. Memantine was assumed to impact the starting static parameters of the equation (baseline ADAS-cog, ADCS-ADL and NPI total scores). The resulting memantine effect from the meta-analysis of the 6 pivotal clinical trials is shown in Table 4.1.

Table 4.1. Memantine effect in the model

Parameter	Mean memantine effect	SD
All targeted patients, moderate to severe AD		
ADAScog baseline	-1.54	0.31
ADCS-ADL baseline	1.53	0.62
NPI baseline	-1.34	0.93
Sub-group with APS		
ADAScog baseline	-2.08	0.59
ADCS-ADL baseline	3.59	0.85
NPI baseline	-2.49	1.65

In order to assess the uncertainty surrounding the effect of memantine on each baseline score, normal distributions were chosen.

4.3.2.2 Probability of Death

The probability of death by month was computed from the LASER-AD cohort modelling mortality as a function of time in patients who were not dependent or institutionalised at baseline, using a Weibull parameterisation (see Appendix N). Probability of death estimations was assumed to be the same for both treatment strategies. Given that no difference was assumed between treatment arms, uncertainty around mortality was not assessed to avoid unnecessary noise around the cost-effectiveness estimates.

4.3.3 Utility

The base case analysis employs utility weights estimated on the UK sample of the LASER-AD cohort. The items on the Twelve-Item Health Status Questionnaire (HSQ-12),¹³⁶ the Ferm's D-test¹³⁷ and the Quality of Life in Alzheimer's disease (QoL-AD)¹³⁸ were mapped into each of the five dimensions of the EuroQoL measure.¹³⁹ The resulting EQ-5D scores were then evaluated with UK tariffs derived from time

trade-off methods¹⁴⁰ to compute utility per patient for each health state (pre-FTC, FTC, death). A full description of the mapping strategy for each modality of the EuroQoL items is provided in Appendix N.

In order to accurately capture the impact of the quality of life of patients during the pre-FTC state and the developing changes as the patient approaches FTC, utilities in the pre-FTC state were linked to the ADCS-ADL score employing a generalised linear model (see Appendix N for details). Utility for the FTC state was calculated using the FTC sub-group of moderate to severe patients from the LASER-AD and was 0.336. Utility for death was assumed equal to 0.

In order to deal with uncertainty surrounding these utilities, normal distributions were used for the FTC utility values, for baseline ADCS-ADL score, and for the memantine effect in the pre-FTC equations.

4.3.4 Costs

4.3.4.1 *Resource Use and Costs Associated with Health States*

Resource use information has been collected for the moderate to severe population (MMSE<20) of the LASER-AD cohort and specified per health state. The Client Service Receipt Inventory (CSRI) has been used in order to capture the resource use with elderly people with AD.¹⁴¹ The CSRI is a questionnaire designed to collect information on formal and informal services received and other aspects relevant to a health economic study. Service usage over the previous three months was recorded from participant responses to the CSRI Interview and, where applicable, from the carer reports. Unit costs for resource use items were taken from the PSSRU 2009.¹⁴² When average contact times were necessary to compute a given unit cost, corresponding data were extracted from the CSRI in the LASER-AD study. Table 4.2 presents the monthly costs. The cost of death was assumed to be zero. In order to assess the uncertainty surrounding monthly costs per health state, gamma distributions were chosen.

Table 4.2. Total monthly cost per health state

Health state	Cost per cycle	
	Mean	SE
Pre-FTC	£724.28	£217.27
FTC	£3267.11	£284.24

Costs were reviewed and discussed in a previous review by SHTAC,¹⁴³ and reported lower estimates: £3,937 per year for pre-FTC and £11,247 per year for FTC patients, assuming 70% of patients are publicly funded, and 52% of FTC is in the community. This cost accounts for institutionalisation and hospitalisation only. Since estimates used in the memantine model, with annual costs of pre-FTC of £8,690 and £39,204 for FTC, are larger, the previous costs estimated by the SHTAC were inflated to 2009 values and used in sensitivity analyses.

4.3.4.2 *Treatment Cost*

According to the British National Formulary,¹⁴⁴ the daily drug dose cost for memantine is £2.16, which equates to a monthly cost of £64.80.

There are also monitoring costs associated with memantine, incurred by all memantine-treated patients before they reach FTC. Monitoring consists of an initial visit to a psychiatrist for treatment initiation then by follow-up visits to the GP every 6 months. The monitoring costs are therefore £124.28 for the first visit (psychiatrist visit for initiation) and £36 for the subsequent visits (GP visit for review).

Cost of AChEI treatment was not included in the model, as it was assumed that the proportion of patients receiving AChEIs is the same in the two treatment arms and would therefore not affect cost differences between the treatments.

4.4 Analyses

In order to describe and compare the evolution of patients, Markov cohort analyses were conducted on both treatment strategies. Costs accrued and QALYs gained by each treatment cohort were recorded and cost-utility analyses were performed calculating incremental cost-effectiveness ratios of memantine treatment versus no treatment for moderate to severe AD patients, as well as for the APS sub-group. The model was designed with both deterministic and probabilistic analysis capabilities and enabled the generation of cost-effectiveness scatter plot and acceptability curves (CEAC).

4.4.1 Parameter Uncertainty

For the probabilistic analysis, normal distributions around baseline characteristics, treatment effects, utility in the FTC health state, and gamma distributions around the costs per health state were used (distribution parameters are reported in the tables above). Monte-Carlo simulation was used to evaluate outcomes based on 10,000 repeated random computations, which attributed a value to each of the a priori distributions. Cost and health outcomes were then estimated and their distribution calculated on the basis of the 10,000 repetitions. This method calculated the probabilities for memantine to be more effective and less costly, therefore making the results dominant, and memantine being cost-effective at both the £20,000 and £30,000 per QALY thresholds.

The cost and outcome calculations were expected to represent the average patient based on the initial distribution of the population in different health states.

4.4.2 Deterministic Scenario Analyses

Two scenario analyses were performed regarding the efficacy of memantine using values derived from two different approaches. In the first scenario, the treatment effects from the 6 pivotal clinical trials were calculated using LOCF data instead of OC in the meta-analysis. In the second scenario, 3 additional clinical trials were included in the meta-analysis using OC data for the total 9 studies. In addition, the cost-effectiveness of memantine as an adjunct therapy was assessed based on the available adjunct clinical trials, (Forest MEM-MD-02, Forest MEM-MD-12), (see Appendix N for further details).

The higher and lower bounds of the 95% confidence intervals of memantine efficacy parameters on each scale (ADAS-cog, ADCS-ADL23 and NPI) were used independently to conduct six scenario-based best and worst case sensitivity analyses. For each of these analyses, one parameter was replaced by the lower or upper bound of its confidence interval, while other parameters remained unchanged compared to base case analysis.

Two scenario analyses were conducted varying the discount rate for costs and health outcomes from 0% to 6% (applied to both costs and health benefits) according to the NICE guidelines.¹⁴⁵

To reflect the fact that not all costs are met by NHS and PSS, costs associated with each health state (pre-FTC and FTC) have been varied +/- 30%.

The sensitivity analyses performed on the utilities variable used 2 alternative sets of data:

- Utilities from the original SHTAC model for AChEIs:¹³¹ 0.34 for FTC, 0.60 for pre-FTC.
- Utilities from the augmented base case and memantine for the treatment of Alzheimer's disease:⁸⁷ 0.34 for FTC, 0.69 for pre-FTC.

The details on calculating utilities are also presented in Appendix N.

4.5 Results

4.5.1 Base Case Results

4.5.1.1 Overall Population with Moderate to Severe AD

The mean survival time in the 5-year model is 47.9 months (44.4 discounted months), and the mean time on drug treatment is 21.1 months. The deterministic base case results for the target population with moderate to severe AD are presented in Table 4.3.

Table 4.3. Base case result – overall population with moderate to severe AD

	Cost (£, 2009)	QALYs	Time in pre-FTC
Memantine	£93,076	1.533	91.4 weeks
Standard care	£94,787	1.502	85.7 weeks
Incremental	-£1,711	0.031	5.6 weeks

In the economic model, treatment with memantine produced on average 39 additional days in the pre-FTC state and 0.031 QALYs over the 5-year evaluation period. These health benefits offset any additional cost associated with memantine treatment and result in cost-savings. Thus, memantine was the dominant strategy compared with standard care.

4.5.1.2 APS Patients with Moderate to Severe AD

As shown in Table 4.4, memantine treatment resulted in 78 additional days or 11.2 weeks in the pre-FTC state and 0.069 QALYs over the 5-year evaluation period compared with standard care in APS patients. Given that memantine was also cost saving compared to standard care, treatment with memantine was the dominant strategy.

Table 4.4. Base case result – APS

	Cost (£, 2009)	QALYs	Time in pre-FTC
Memantine	£93,845	1.563	90.0 weeks
Standard care	£98,816	1.493	78.8 weeks
Incremental	-£4,971	0.069	11.2 weeks

4.5.2 Sensitivity Analyses

In order to assess the robustness of the results and the conclusions of the economic model a large set of sensitivity analyses were performed on both the overall population with moderate to severe AD and the APS sub-group.

4.5.2.1 Overall Population with Moderate to Severe AD

The probabilistic module calculated the mean and the standard deviation for total discounted costs over the model time horizon as shown in Table 4.5.

Table 4.5. Base case result probabilistic – overall population with moderate to severe AD

Treatment	Memantine	Standard care	Incremental
Total costs (discounted) (£)			
Probabilistic Mean	92,971	94,687	-£1,716
Standard Deviation	9,022	9,099	
2.5% and 97.5% percentile	76,450 to 111,735	77,889 to 113,523	
QALYs			
Probabilistic Mean	1.534	1.503	0.031
Standard Deviation	0.095	0.097	
2.5% and 97.5% percentile	1.339 to 1.712	1.306 to 1.687	
Time in pre-FTC (Weeks)			
Probabilistic Mean	91.6	85.9	5.6
Standard Deviation	7.3	6.9	
2.5% and 97.5% percentile	77.6 to 106.2	72.7 to 99.8	

The cost-effectiveness scatter plot (Figure 4.2) shows the results from the probabilistic analysis of the economic model with a 96.4% probability of memantine being less costly compared to standard care and 99.8% probability of memantine being more effective.

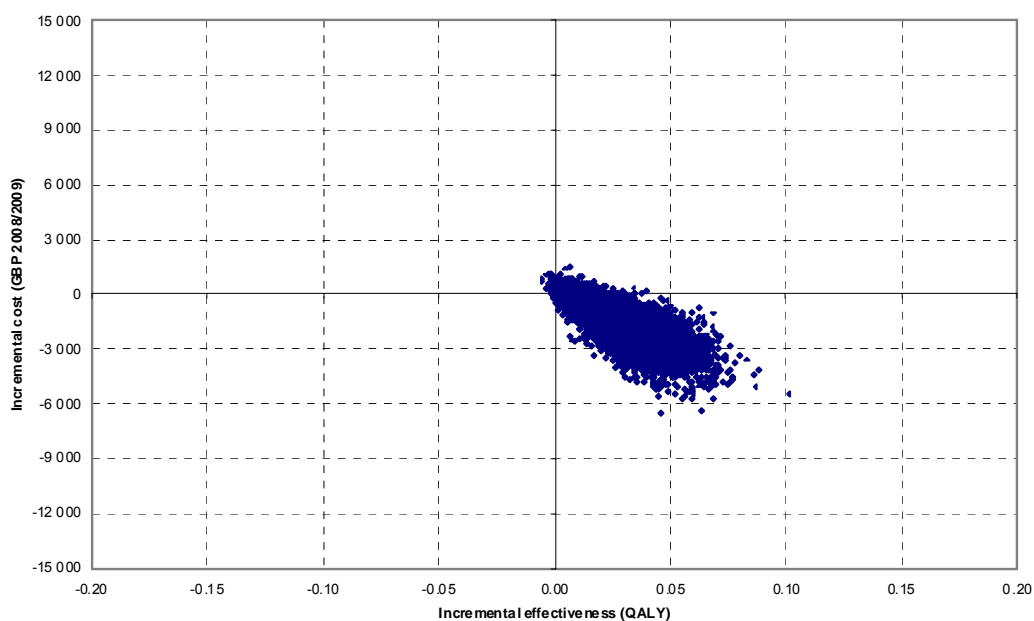
Figure 4.2. Cost-effectiveness scatter plot in overall population with moderate to severe AD

Table 4.6 reports selected one-way sensitivity analysis to address uncertainty in parameters.

Overall uncertainty around model outcomes was assessed using stochastic analyses. Influence of treatment effect estimation was assessed by using alternative estimation methods (LOCF, inclusion of additional studies or adjunct studies only) and by varying each efficacy parameter (ADAS-cog, ADCS-ADL23 and NPI) on the whole width of their confidence interval. Costs associated to each health state were varied by +/-30% and alternative sets of utilities were tested. In line with recommendations, discount rates for costs and health benefits were also varied between 0% and 6%.

Table 4.6. Summary of sensitivity analyses – overall population

Incremental cost and outcomes	Cost	QALYs	Time in pre-FTC
BASE CASE	-£1,711	0.031	5.6 weeks
Stochastic analysis	-£1,716	0.031	5.7 weeks
Treatment effect – LOCF	-£1,587	0.027	5.4 weeks
Treatment effect – OC + 3 additional trials	-£1,373	0.027	5.0 weeks
Treatment effect – Adjuvant trials only	-£1,576	0.026	5.4 weeks
Treatment effect on cognition: best case	-£1,990	0.031	6.1 weeks
Treatment effect on cognition: worst case	-£1,433	0.030	5.1 weeks
Treatment effect on disability: best case	-£3,200	0.053	8.3 weeks
Treatment effect on disability: worst case	-£242	0.009	3.1 weeks
Treatment effect on behaviour: best case	-£2,669	0.034	7.3 weeks
Treatment effect on behaviour: worst case	-£761	0.028	4.0 weeks
Discount rate 0%	-£1,890	0.032	6.0 weeks
Discount rate 6%	-£1,595	0.030	5.4 weeks
Cost Pre-FTC -30%	-£1,994	0.031	5.6 weeks
Cost Pre-FTC +30%	-£1,428	0.031	5.6 weeks
Cost FTC -30%	-£435	0.031	5.6 weeks
Cost FTC +30%	-£2,987	0.031	5.6 weeks
Alternative set of utilities (0.34/0.60)	-£1,711	0.028	5.6 weeks
Alternative set of utilities (0.34/0.69)	-£1,711	0.038	5.6 weeks

Additional sensitivity analyses on the costs and utilities were performed and alternative inputs (costs and utilities) from the previous SHTAC model for AChEIs¹³¹ were tested: see Appendix N.

Using different sets of RCTs or different statistical methods to measure efficacy had limited effect on costs and QALYs. Conclusions remain unchanged when using alternative inputs for costs or utilities for pre-FTC and FTC states.

From the sensitivity analyses, the results are shown to be sensitive to a range of alternative inputs for effectiveness as measured by functioning and behaviour, and to cost inputs for FTC. However, when assuming that all memantine-treated patients would receive minimum benefit on functioning, memantine remains a cost-effective alternative.

The economic model was sensitive to changes in FTC annual costs; however memantine remains cost neutral even when costs of FTC are reduced by 30%. Using previous estimates from the SHTAC Assessment Group resulted in lower costs for pre-FTC and memantine remains cost-effective with an incremental cost per QALY of £21,700.

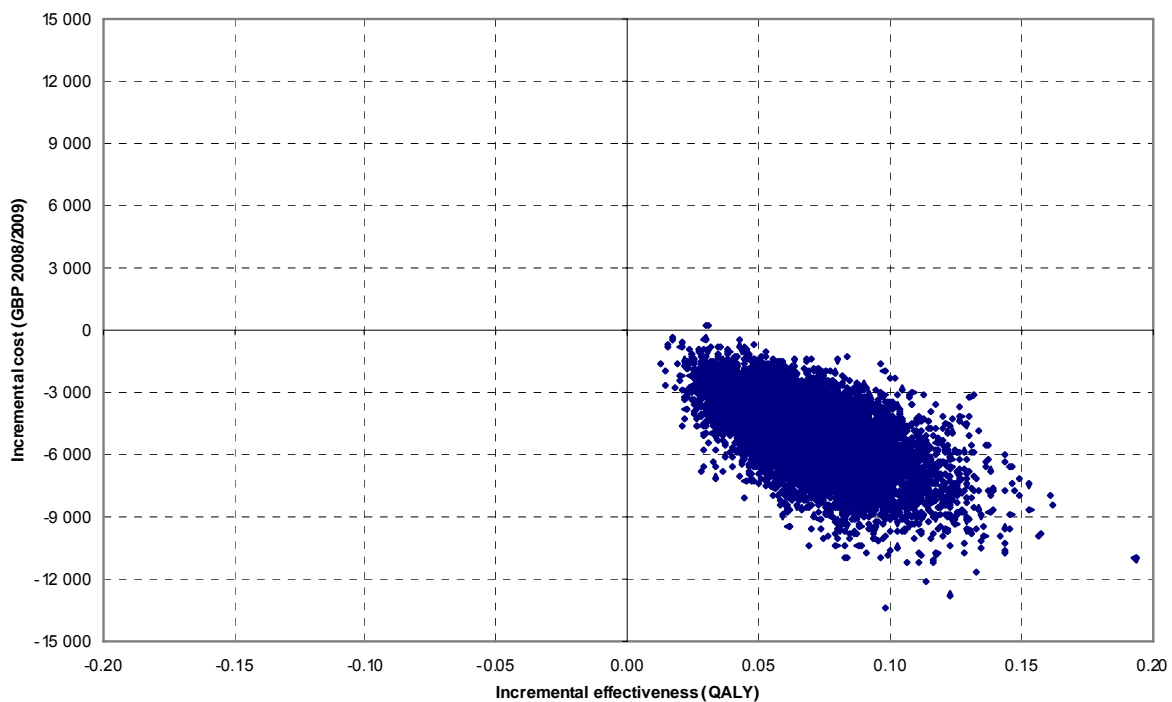
4.5.2.2 APS Patients

For the APS sub-group analyses, the stochastic analysis results were similar to those obtained with the deterministic analysis. Table 4.7 provides descriptive statistics of cost and effectiveness results by treatment strategy and corresponding incremental differences.

Table 4.7. Base case results probabilistic - APS

Treatment	Memantine	Standard care	Incremental
Total costs (discounted) (£)			
Probabilistic Mean	£93,663	£98,639	-£4,976
Standard Deviation	£9,700	£9,772	
2.5% and 97.5% percentile	75,687 to 113,540	80,634 to 118,586	
QALYs			
Probabilistic Mean	1.566	1.496	0.070
Standard Deviation	0.104	0.106	
2.5% and 97.5% percentile	1.351 to 1.760	1.279 to 1.696	
Time in pre-FTC (Weeks)			
Probabilistic Mean	90.3	79.1	11.2
Standard Deviation	9.5	8.6	
2.5% and 97.5% percentile	72.4 to 109.7	62.9 to 96.7	

Memantine was dominant compared to standard care in 99.98% of the simulations as confirmed by the cost-effectiveness scatter plot shown in Figure 4.3.

Figure 4.3. Cost-effectiveness scatter plot in the APS sub-group

Deterministic sensitivity analyses in the APS sub-group were performed around the same parameters as the overall population with moderate to severe AD (see Table 4.8). In addition, the impact of the ADAS-Cog and ADCS-ADL slope estimates was explored both deterministically and stochastically.

Table 4.8. Summary of sensitivity analyses - APS

Incremental cost and outcomes	Cost	QALYs	Time in pre-FTC
BASE CASE	-£4,971	0.069	11.2 weeks
Stochastic analysis	-£4,976	0.070	11.2 weeks
Treatment effect – LOCF	-£4,015	0.052	9.5 weeks
Treatment effect – OC + 3 additional trials	-£4,412	0.067	10.2 weeks
Treatment effect on cognition: best case	-£5,498	0.071	12.1 weeks
Treatment effect on cognition: worst case	-£4,447	0.067	10.2 weeks
Treatment effect on disability: best case	-£7,003	0.100	14.7 weeks
Treatment effect on disability: worst case	-£2,977	0.039	7.6 weeks
Treatment effect on behaviour: best case	-£6,664	0.075	14.1 weeks
Treatment effect on behaviour: worst case	-£3,304	0.063	8.2 weeks
Discount rate 0%	-£5,357	0.072	11.9 weeks
Discount rate 6%	-£4,720	0.067	10.7 weeks
Cost Pre-FTC -30%	-£5,531	0.069	11.2 weeks
Cost Pre-FTC +30%	-£4,411	0.069	11.2 weeks
Cost FTC -30%	-£2,447	0.069	11.2 weeks
Cost FTC +30%	-£7,495	0.069	11.2 weeks
Alternative set of utilities (0.34/0.60)	-£4,971	0.056	11.2 weeks
Alternative set of utilities (0.34/0.69)	-£4,971	0.075	11.2 weeks
General population slopes – deterministic	-£5,008	0.071	11.3 weeks
General population slopes – stochastic	-£5,017	0.071	11.3 weeks

4.6 Discussion

In order to review the limitations of the current economic model, the same structure for discussion was used as in the review of modelling methods used for cost-effectiveness in AD by Green et al., i.e. focussing on four main areas to assess the elements “essential for the delivery of a good-quality model”: model structure, data, consideration of uncertainty and consistency.¹²⁷

Model structure

In the review by Green, it was noted that there was typically a lack of rationale provided for the choice of model structure. Green also highlighted that the main concern was the reliance on the use of cognition only to model disease progression over time. The current structure of the memantine model fundamentally relies on the same assumption of previous models, essentially the AHEAD model¹²⁵ and its further adaptation by the SHTAC group.¹³¹ The rationale for using the FTC and pre-FTC to model disease progression for moderate to severe AD is therefore logical to assess the effect of treatment, and is based on a large body of evidence that FTC and pre-FTC are clinically and economical relevant states. Other economic models have used time to institutionalisation, time to severe AD or time to dependency as outcomes. For memantine, since patients may be already severe, these outcomes are clearly insufficient to assess the benefits of memantine.

FTC and pre-FTC on the other hand are more relevant outcomes to measure the effect of memantine in a moderate to severe AD population. The previous economic model for memantine made an attempt to include outcomes other than cognition to measure the treatment effect. However, there were some limitations as the outcome dependency was derived from cluster analysis¹⁴⁶ hence more difficult to reproduce for other treatments and, therefore, was more difficult to interpret.

In addition to being a relevant outcome to model disease progression of AD in a more severe population, FTC and pre-FTC are relevant states from both a clinical and an economic perspective. Indeed, in the SHTAC report of 2002, the assessment group noted that “The structure of the economic model involves only two AD states (i.e. pre-FTC, FTC) and this may be seen as a crude reflection of the natural history of AD. However, the health states used can be regarded as those of interest, and may reflect a more policy-orientated view of AD than plotting stages of disease severity that are difficult to align to policy relevant outcomes”.

We defined FTC patients who were dependent⁶² and/or institutionalised. Pre-FTC patients do not only incur lower costs, but are significantly less impaired on the three main domains in AD: cognition, ADL and behaviour.

The current economic model addresses two essential limitations of the previous model using FTC and predictive equations:

- The predictive equations used in the memantine model (Appendix O) include additional factors on top of cognition that are known to influence disease progression: behaviour and ADL. Whilst behaviour was somewhat incorporated in the AHEAD model, this is to our knowledge the first attempt to incorporate ADL in a predictive equation to our knowledge;
- Generalisability of data. The previous AHEAD model was based on a US cohort, whilst the predictive equations are based on a UK cohort with 4.5 years of follow up.

The economic model does not include considerations of dropouts from treatment, because the drop out rates were similar between memantine and placebo (while drop out tends to be higher for AChEIs). In order to have a proxy of the impact of drop out, sensitivity analyses were performed using both LOCF or OC methods and did not show major differences between the two approaches thus confirming that the non inclusion of drop out in the memantine model does not lead to an overestimation of the benefit.

Data

The review by Green et al.¹²⁷, highlighted two key issues in addition to the traditional limitations of modelling that combine different sources of data: measurement of QALY and the appropriateness of the effectiveness data used. In addition we reviewed the different sources of resource use and costs for FTC and pre-FTC.

QALY

There is still a challenge in assessing utilities for states of AD given the lack of direct evidence, as well as limitations in existing studies that associate health utilities and levels of FTC in AD.

The limitation highlighted by Green for the previous memantine model was the use of QALYs derived from a sample of patients who were mostly independent with mild AD for a targeted population of moderately severe to severe patients. The current model derived QALYs from a more representative UK sample of moderate to severe patients with representative distribution of FTC and pre-FTC. Since utilities were not measured directly by EuroQoL or direct measurement, a mapping to derive the utilities was used. This method has limitations, but the utility estimates around FTC and pre-FTC are consistent across sources (Table 4.9) and different measurements, which increases the reliability of our estimates.

Table 4.9. Health utilities between dependency and non-dependency states

Authors	Utility		Difference	Instrument	Sources
	Pre-FTC	FTC			
Andersen, 2004 ¹⁴⁷	0.64	0.34	0.30	EuroQoL (mapping)	Denmark
Sapin, 2005 ¹³⁹	0.60	0.25	0.35	EuroQoL (mapping)	UK
Ward, 2003 ¹⁴⁸	0.60	0.34	0.26	HUI2	USA
Neumann, 2004 ¹⁴⁹	0.62	0.34	0.28	HUI2	USA

In addition different values have been used in the sensitivity analyses to estimate the impact of the choice of QALY.

Costs

The costs estimated from the LASER-AD study are higher than other published data on AD. This can be explained by different factors:

- The cost of FTC has been calculated in moderate to severe only, while the previous estimate from SHTAC was based on mild to severe. Specifically, 70% of the sample was institutionalised vs. 48% in the SHTAC report. If we use a simple calculation, using latest data from Netten for private nursing homes (£575 from NHS and PSS perspective), a patient institutionalised for one year would cost £29,900, which is a closer estimate to that observed in the LASER-AD study.
- Data collected from LASER-AD used a validated resource use questionnaire, the CSRI, and included many types of resource use, such as hospitalisation. It is clear that including hospitalisation in FTC increases the total costs, though some hospitalisations may not be directly related to AD. Thus AD treatment would have an undue effect and therefore overestimates the benefits in terms of costs. However, it would be impossible to assess which costs are related to AD or not so they were included in our estimate.
- The cost estimates are based on a 3-month recall period, which may have introduced recall bias and measurement error. However, it is not clear whether this will tend to over and underestimate the reporting of resource use. This problem is similar to previous surveys which estimated costs in AD.
- The LASER-AD study was observational, and there is a legitimate question about whether it is representative. There was a stratification to ensure AD population would be represented according to the epidemiology of the disease. It is possible, however, that the geographical location of the study (London and South East Region) is not representative of the entire UK.
- Previous estimates of the cost of FTC and non-FTC combined data from different studies has varied (multiple sources), but one potential reason is that some of the sources include a relatively old study.¹⁵⁰ It is known that since there has been a change in the provision of dementia services, this survey may underestimate the current costs. Also, it is not clear how the FTC cost relates to functional impairment as the data source did not include measurement of functional disability, but cognitive impairment (e.g. OPCS survey). Calculating FTC based on cognition and not ADL may also underestimate costs.
- Finally, the costs used in the memantine model may not fully take into account that not all costs are met by the NHS and PSS, with some patients in an institutional setting receiving partially private funding, and that some of the costs may be actually transfer costs.

In summary, therefore it is difficult to fully appreciate whether our figures of costs per FTC are overestimated or whether the previous figures are underestimated. There are probably limitations in both. In any case, sensitivity analyses using the previous FTC estimates from SHTAC did not change the conclusion: while the offset on other costs no longer offset the cost of memantine, the cost per QALY remains below £30,000 for the moderate to severe population, and below £5,000 for the APS sub-group.

Appropriateness of the effectiveness data used

One previous limitation of the donepezil and memantine models highlighted by Green et al.,¹²⁷ was the difficulty for the reader to reconcile the effectiveness data presented in the clinical section and the transition probabilities used in the model. The current economic model clearly addresses this limitation. The estimates of treatment effects are clearly presented, and are directly implemented in the predictive equations, so the reader can now directly link the clinical effectiveness data with the cost-effectiveness analyses. In addition, we have presented the rationale for pooling the results of the different clinical trials in both moderate and severe AD, as well as in monotherapy or adjunct therapy.

Uncertainty and Inconsistency

Using the same approach by Green et al.,¹²⁷ the four principal types of uncertainty are described below: methodological, structural, heterogeneity and parameter uncertainty

Methodological and structural

Compared to previous memantine models which assumed an extrapolation of treatment effect to over a year,¹²⁷ we used a more conservative estimate of treatment effect, in the sense that the treatment effect

matched the exact duration of the RCTs, i.e. six months. Since other data may support longer effect of memantine^{114, 151} the model may be conservative in that regard.

With regards to the structure, Green et al.¹²⁷ urged a more holistic approach that would capture the broad nature of AD (i.e. functioning, cognition and behaviour). While pre-FTC and FTC may be seen as too simplistic at first sight, they do encompass the broad nature of AD. Also all three domains are now incorporated in the predictive equations.

Our results are consistent with previous Markov modelling that investigated the cost-effectiveness of memantine in monotherapy versus no pharmacotherapy in moderate to severe AD in various countries with a different model framework.¹⁵²⁻¹⁵⁶ Compared with other cost-utility evaluations performed for other drugs in mild-to-moderate AD, the benefit of memantine in terms of QALYs is within the same range.^{148, 157}

Heterogeneity

We presented an analysis of the APS sub-group, as there is evidence that these patients have more rapid decline, are more impaired and incur higher costs. Memantine effectiveness was significantly better and associated with lower costs and more QALYs in this sub-group compared to the general moderate to severe population.

The effect of memantine in decreasing antipsychotic prescribing has also been demonstrated in real practice which supports this benefit on behavioural disturbance observed in clinical trials. This was demonstrated consistently in three different large epidemiological studies, including one driven by the French authorities.^{112, 113, 115}

Parameter uncertainty

This uncertainty was explored in a series of both one-way and probabilistic sensitivity analyses, comprehensively covering the uncertainty around the parameters. Assumptions and inputs used in the model, such as utilities and transition probabilities, were tested by sensitivity analyses. Probabilistic cost-effectiveness modelling overcomes the shortcomings of more simplistic sensitivity analysis by allowing uncertainty in all parameters of the model to be considered, as well as helping to determine the joint effects of costs and effectiveness.¹⁵⁸ Moreover, additional one-way sensitivity analyses confirmed the internal validity of the model since the results varied in the expected way.

In conclusion, the current economic model presents several areas of improvement:

- The effect of memantine modelled is based on a large set of RCTs in the moderate to severe AD population, which results in lower uncertainty around the cost/QALY.
- The model structure is using the same framework as the previous SHTAC and AHEAD models, with the further inclusion of ADL and Behaviour in addition to Cognition to model treatment effect.
- The model is based on a representative sample of UK AD patients from the LASER-AD study instead of the US cohort.

4.7 Implications of Model Results

The model results demonstrate clearly and consistently that memantine is cost-effective for both the overall population and the APS sub-group across a wide range of assumptions. As far as practicable, the epidemiological data in the model was derived from the LASER-AD study making these findings directly relevant to the UK population. The results of memantine incurring less costs and offering greater health benefits compared to standard care is consistent with all publications describing the cost-effectiveness of memantine as being either cost neutral¹⁵⁶ or cost saving.^{152-155, 159, 160}

5.0 WIDER IMPLICATIONS

KEY POINTS

- By 2015, 206,273 people in the UK are estimated to develop moderate to severe Alzheimer's disease
 - It is expected that 133,195 patients could be eligible for the memantine-targeted population
 - It is expected that 59,299 will belong to the APS sub-group and 16,604 of these will use antipsychotics inappropriately
 - Memantine could replace inappropriate use of antipsychotics
 - The net budget impact for the overall population is estimated at £32,300,000 over five years. Targeting the incident APS sub-group would not put extra burden on NHS resources, but would ensure that the population most likely to benefit receives treatment
- The implementation of extended use of memantine is expected to have negligible impact on the use of NHS and PSS resources:
- Memantine would bring about major resource savings associated with delayed institutionalisation, lower levels of needed care, and avoidance of antipsychotic treatments with a positive impact on the quality of life of both patients and carers.
- Memantine therapy further supports NICE objectives in promoting social values related to age, individual choice, stigma, equality and disability/quality of life

Not adopting memantine in the NHS would deny AD patients an effective alternative to inappropriate AP therapy.

5.1 Budget Impact

5.1.1 Eligible Population

To calculate the number eligible patients who could be using memantine, the following data were used and assumptions made:

- The size of the patient cohort above the age of 65 for each year between 2010 and 2014 was taken from the population projection of the Office of National Statistics (2008)¹⁶¹
- The prevalence of AD in this population was assumed to be 3.83%⁴⁰
- The incidence of AD in this population was 4.9 per 1,000 person-years.⁴² The simplifying assumption was also made that all new AD patients will reach the moderate or severe stage in the same year
- 31% of AD patients is assumed to have moderate disease, while 21% is assumed to have severe disease⁴⁵
- The Cochrane review of AChEIs estimated that approximately 29% discontinued treatment on account of adverse events.⁶⁷ We assumed that 10% of moderate patients would be ineligible for AChEIs therapy. These two patient groups make up the population eligible for memantine monotherapy in patients with moderate AD. Furthermore, 7% of patients on AChEIs may receive adjunct treatment with memantine (GPRD data on file)
- It was assumed that all new patients eligible for treatment would be treated with memantine to fully capture the impact of a positive recommendation by NICE. In comparison a recent study estimated only 56% of eligible AD patients were receiving treatment (Cognos Study 6 Alzheimer's Disease, Decision Resources)

- The proportion of patients within the moderate to severe AD population who also qualify for the APS sub-group was determined from the LASER-AD study, where 65 out of 146 (44.52%) moderate to severe AD patients had APS using the criteria described in section 2.6.

The estimated numbers of patients are show in Table 5.1.

Table 5.1. Estimated patient numbers by year

Year	2011	2012	2013	2014	2015
General population >65	9,325,769	9,641,804	9,922,264	10,150,751	10,357,132
Population with moderate-severe Alzheimer's dementia	185,732	192,026	197,612	202,162	206,273
Population with moderate-severe AD eligible for memantine	119,932	123,996	127,603	130,541	133,195
Population with moderate-severe AD - APS	53,394	55,204	56,809	58,118	59,299
Population with moderate-severe AD - APS plus inappropriate AP use	14,950	15,457	15,907	16,273	16,604
Incident population with moderate-severe AD	23,762	24,567	25,282	25,864	26,390
Incident population with moderate-severe AD eligible for memantine	14,710	15,209	15,651	16,011	16,337
Incident population with moderate-severe AD – APS	6,549	6,771	6,968	7,128	7,273
Incident population with moderate-severe AD - APS plus inappropriate AP use	1,834	1,896	1,951	1,996	2,037

Legend: AP – antipsychotics

Memantine could replace the inappropriate use of antipsychotics in the APS sub-group. Based on an audit of prescribing practice in a specialist psychiatric inpatients unit, 56% of APS patients were assumed to be treated with antipsychotics.¹⁶² As a conservative assumption, 50% of AP prescribing is assumed to be inappropriate. A recent report by the All Party Parliamentary Group on Dementia supports a level of 50-70% of antipsychotics prescriptions being inappropriate in this population.¹⁶³ Table 5.1 also shows the number of patients estimated to receive antipsychotics inappropriately.

5.1.2 Annual Drug Costs

The current cost of memantine per day of treatment is £2.16 regardless of the formulation, making the annual cost of treatment £788.40.¹⁴⁴ Memantine's patent expires in April 2014. Its price is expected to decrease by 80%, therefore the annual cost for the year 2015 was assumed to be £157.68. The average length of treatment was estimated to be 16 months from prescription data (on file).

To calculate the cost of inappropriate AP treatment, the type of drugs, doses and proportions of patients receiving them were pooled (using simple averages) from two studies.¹⁶⁴ Drug costs were sourced from the BNF (2009),¹⁴⁴ making the weighted average annual cost of antipsychotic treatment assuming continuous treatment £135.60 in this population.

5.1.3 Budget Impact Scenarios

Four different scenarios were compared against a base-case scenario to determine the new budget impact of a positive recommendation on memantine. The base-case scenario assumed no change in the current recommendation. The 2009 sales of memantine were £6,906,455 (Lundbeck sales information), while Anti-Alzheimer's market sales have grown 10.8% in the last year. The prescribing of drugs for AD has continued to increase since the introduction of the latest guidance. The latest NICE uptake report

(2009)¹⁶⁵ identified an increase in the prevalence of AD as the main source of this increase. To account for this fact, the base-case scenario assumed that the proportion of patients treated with memantine will remain the same, i.e. sales will continue to grow at the same rate as the patient population. Resulting annual budgets are shown in Table 5.2 totalling to about £31,640,000 over five years. Since there is no information on the characteristics of patients currently receiving memantine, the metric of equivalent patient-years on treatment (calculated as total annual expenditure divided by the annual treatment cost of memantine) was created to enable comparison with the other predicted treatment scenarios.

Table 5.2. Budget impact of different uptake scenarios

Year	2011	2012	2013	2014	2015	Total over 5 yrs
Basecase: No change in recommendation						
Budget impact	£7,177,077	£7,420,296	£7,636,137	£7,811,980	£1,594,162	£31,639,651
Equivalent patient-years on treatment	9,103	9,412	9,686	9,909	10,110	
Scenario 1: All new eligible mod to severe patients start treatment with memantine (no AP off-set)						
Number of patients starting treatment	14,710	15,209	15,651	16,011	16,337	
Budget impact	£11,597,432	£15,856,260	£16,336,043	£16,736,446	£3,417,563	£63,943,744
Equivalent patient-years on treatment	14,710	20,112	20,721	21,228	21,674	
Net budget impact compared to no change	£4,420,355	£8,435,964	£8,699,906	£8,924,467	£1,823,401	£32,304,093
Scenario 2: All new eligible APS mod to severe patients start treatment with memantine (no AP off-set)						
Number of patients starting treatment	6,549	6,771	6,968	7,128	7,273	
Budget impact	£5,163,240	£7,059,294	£7,272,896	£7,451,158	£1,521,5181	£28,468,105
Equivalent patient-years on treatment	6,549	8,954	9,225	9,451	9,649	
Net budget impact compared to no change	-£2,013,837	-£361,002	-£363,241	-£360,822	-£72,644	-£3,171,546
Scenario 3: All new eligible mod to severe patients start treatment with memantine (AP off-set)						
Number of patients starting treatment	14,710	15,209	15,651	16,011	16,337	
Budget impact	£11,348,777	£15,516,295	£15,985,791	£16,377,609	£3,051,192	£62,279,664
Net budget impact compared to no change	£4,171,701	£8,095,999	£8,349,654	£8,565,630	£1,457,030	£30,640,013
Scenario 4: All new eligible APS mod to severe patients start treatment with memantine (AP off-set)						
Number of patients starting treatment	6,549	6,771	6,968	7,128	7,273	
Budget impact	£4,914,5869	£6,719,328	£6,922,644	£7,092,321	£1,155,147	£26,804,026
Net budget impact compared to no change	-£2,262,491	-£700,968	-£713,493	-£719,659	-£439,015	-£4,835,625

Scenario 1 assumed that all new patients with moderate to severe AD eligible for memantine treatment (ineligible for, switching from, or in addition to AChEIs in moderate AD, or in severe AD) receive the treatment. The equivalent patient years treated increases by about 50% compared to the no change in recommendation scenario, and total budget impact also increases to about £16,000,000 annually and to £63,940,000 over five years, making the net budget impact compared to the base-case about £32,300,000.

Scenario 2 applied the same assumptions as scenario 1 to the incident patients in the APS sub-group. The total budget impact is £28,470,000 over five years, roughly matching predicted sales and the equivalent patient-years of treatment in the base case scenario. However, the patient group receiving treatment would be the ones who actually benefit most from treatment.

Scenario 3 is identical to scenario 1 in considering all new eligible patients with moderate to severe AD. However, in this scenario memantine is assumed replace inappropriate prescription of antipsychotics in the population receiving antipsychotics inappropriately for the duration of treatment. This reduces the five year budget requirement by £1,660,000, making the total impact £62,280,000, and the net budget impact £30,640,000.

Scenario 4 applied the same assumption on the impact of memantine on inappropriate antipsychotic prescriptions to the new APS patients, and resulted in £26,800,000 total budget impact and a saving of £4,800,000 over the base case scenario over five years.

5.2 Service Impact

5.2.1 Implementation of New Guidelines in Moderate to Severe Patients Have Minimal Net Impact

The extended use of memantine is expected to have a negligible impact on the use of NHS and PSS resources. Patients are typically diagnosed with AD long before they reach the moderate to severe stage so appropriately identifying eligibility criteria for memantine would be performed as part of a routine patient care programme for established patients. This patient care programme would be expected to evolve naturally to meet the increasing needs of a declining patient and the introduction of memantine is a natural step in recognising patient progression and would not be expected to add meaningfully to provider burden. Additional physician visits for assessing patient suitability would not be required in the majority of cases and costly diagnostics such as CT scanning is more likely to occur in the mild to moderate AD patients. The only exception to this is that APS patients would need to be assessed using the NPI scale to determine suitability. However, this is already common practice in many clinics and does not place a heavy burden on NHS staff. Due to memantine's favourable adverse event profile compared to placebo, there would be few drug-related episodes to manage. For many patients, introduction of treatment will be undertaken in the context of a shared care protocol that reflects the current emphasis being placed on a primary care-led NHS. The use of memantine therefore makes few additional demands on NHS resources.

5.2.2 Positive Service Impact

One of the major effects of memantine is the resource savings associated with the delayed institutionalisation and antipsychotic treatments avoided. As suggested by the cost-effectiveness model, this would result in a positive service impact both in terms of delayed institutionalisation and lower levels of care required. This could also be expected to increase the quality of life of both patients and carers. By not adopting memantine in the NHS, there would be a negative service impact, particularly surrounding institutionalisation. This would also deny patients an effective alternative to inappropriate antipsychotic therapy.

5.3 Wider Considerations

5.3.1 Introduction

NICE states that one of its guiding principles is that 'Decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone. NICE must consider other factors when developing its guidance, including the need to distribute health resources in the fairest way

within society as a whole'.¹⁶⁶ With this in mind, there are several social considerations that are relevant to AD patients, including those eligible for memantine.

5.3.2 Age

AD incidence increases with age, and so this factor should be taken into account.

The *National Service Framework for Older People*¹⁶⁷ recognizes the importance of elderly people maintaining independence for as long as possible so that they can continue to live at home rather than in costly acute hospital beds or long-term institutional care. It also recognizes the valuable contribution that carers make in this respect.

Memantine specifically targets elderly patients with the most severe need, and so its more widespread availability represents an opportunity to both target additional resources on a disease that largely afflicts this age group and address the issue of age discrimination in the distribution of NHS resources.

5.3.3 Individual Choice

Individual choice and patient preferences are an important issue in those suffering from dementia whether it be from early stage dementia or a later, more advanced stage. The aim of providing person centred care, regardless of age and on the basis of need alone, implies that older people should receive appropriate care packages that are tailored to their individual needs. Such an aim implies that people with severe AD should not be neglected, and that having memantine available represents an important aspect of the clinical need of these patients. Memantine provides an important aspect of end of life care and could be important in improving the quality of life for both patients and carers in a number of different ways.

Sufferers of dementia are "known to be an 'at risk' group in terms of abuse, in particular through financial exploitation, fraud and theft".¹⁶⁸ In addition to this, the complexities involved in the relationships between carers and patients mean that patients do not always report incidences of abuse or mistreatment, which can become further complicated if the patient does not have the capacity to make this known.¹⁶⁸ Availability of memantine could help to reduce the level of risk by helping dementia sufferers communicate problems more easily and make them less prone to being taken advantage of.

There have been widespread concerns and criticism of the use of AP medication in care homes in the management of behavioural and psychological symptoms. This is due to the increased risks associated with these medications in dementia patients.¹⁶⁸ Memantine can improve behavioural symptoms which could reduce the need for AP drugs, thus reducing the risks associated with them such as increased mortality and stroke, in addition to providing a treatment option that has been previously not recommended by NICE. Putting People First (DoH, 2007)¹⁶⁹ advocates a personalised adult social care system which can work for people with dementia as well as those without cognitive impairment. It sets out the agenda to give more choice and control to people who use services, including people with dementia, saying "It is important for people with dementia to have choice and control over when and what is offered, as people can be best reassured through familiar faces and responses as allowed by their memories and experiences." Personalised services and choice are key themes of the Government's New Horizons (DoH, 2009)¹⁷⁰ vision for mental health services: "People with mental health problems, and those at risk, will receive personalised care packages designed to meet their individual needs. They will be able to make decisions about their care, treatment and goals for recovery, as well as to monitor their own condition."

5.3.4 Conditions Associated with Stigma

Objective 1 of the National Dementia Strategy addresses the issue of stigma by looking to improve public and professional awareness and understanding of dementia. This should inform individuals of the benefits of timely diagnosis and care, promote the prevention of dementia, and reduce social exclusion and discrimination. It should encourage behavioural change in terms of appropriate help-seeking and help provision.

The lack of understanding and awareness in the professional setting can lead to the routine under-diagnosis of dementia or misattribution of symptoms to just being a part of old age.¹⁶⁸ This is important because it may mean that the condition is left to progress where appropriate care and therapy could have delayed onset and helped manage already worsening conditions. This is not restricted to GPs but is also relevant in hospitals, often dementia goes undiagnosed and families are not involved in discharge planning, and it is therefore not taken into account whether the home environment is fit for the person with dementia. The NAO¹⁶⁸ found that some general hospital services preferred not to make the diagnosis of dementia, for fear it would delay discharge.

Reducing stigma and improving understanding is a key theme of the New Horizons¹⁷⁰ vision for mental health services. It says “Older people with mental health problems can be among the most socially excluded in society. The stigma of old age is amplified by the stigma of having a mental health problem, and may be further compounded by physical health problems and disabilities.”

Memantine enables patients to retain their independence for longer, while maintaining many of their daily activities, such as standing up and moving about, getting dressed, eating, drinking and using the toilet. It may thus facilitate the return home of people with advanced dementia following acute hospitalisation. The improved ability to function and communicate could help in dispelling some of the traditional stigma associated with the disease.

5.3.5 Avoiding Discrimination and Promoting Equality

Age discrimination within healthcare provision has been highlighted as being unacceptable in a range of government policy publications, including the *NSF for Older People* (DoH, 2001)¹⁶⁷ and the *National Dementia Strategy*.

According to *New Horizons*,¹⁷⁰ there is evidence that older people can experience discrimination and inequity in access to and availability of mental health services, and can experience poorer quality of care than working age adults. Older people also typically present with more complex needs.

They are more likely to have:

- Multiple care needs for a range of co-existing problems
- Physical and mental health and social care needs
- Different patterns of social care and family support
- Specific problems such as dementia.

Use of the QALY in a patient population of elderly patients with moderately severe to severe AD (a vulnerable social group) is insufficient to reflect the full health outcome.¹⁷¹ Age, disease severity and/or care setting should not be used as grounds to restrict memantine therapy. As far as severe AD is concerned, it is appropriate and fair to incorporate an equity weighting into the health economic evaluation.

The issue of pain provides an example of the discriminatory care provided for dementia patients. Dementia patients receive less analgesia than other elderly patients.¹⁷² The illness may mean that a patient is incapable of making themselves understood, and that some of the frustrated and aggressive behaviour which occurs more frequently in late stage dementia could well be an expression of pain. People with dementia admitted to hospital for hip fracture with the same surgical intervention were given less than half the pain relief of those with normal cognitive functioning.¹⁶⁸ The majority of those with dementia had severe postoperative pain which was not actively managed. “Communication problems in dementia may lead staff to ‘surmise that pain not expressed is pain not experienced’ and that pain expressed as aggression or confusion may lead to labelling and management as ‘difficult’.”¹⁶⁸

Equity with regard to treatment location is also essential. Memantine plays a crucial role in supporting patients in the community, but it is equally important to acknowledge its role in the institutional environment. Institutional care is a fundamental element in the spectrum of support for some patients with severe AD, and improving treatment and enhancing quality of life is as important in this setting as it is in

the community. As welfare gains in the institutional setting are comparable with those gained in the community, memantine should be equally available to both groups of patients. Provision of memantine may also contribute to cost containment if it reduces the need for close staff supervision for a number of institutionalised patients.

There is a need to ensure vertical equity in the treatment of patients exhibiting different levels of need. As the severity of AD increases, there will be a commensurate increase in the level of support required by both patients and carers. As their level of need increases, vertical equity requires service providers to implement additional services wherever possible. Memantine would provide valuable support to patients at their time of greatest need and there is currently no evidence to suggest that the capacity of the drug to benefit the majority of AD patients is reduced as the severity of the disease increases.

Promoting equality and tackling discrimination are key themes of the Government's New Horizons vision for mental health services: "In 2020 all individuals will be treated with respect in an inclusive society, whatever their age, background or circumstances. Public services will maximize the importance of environments, services and amenities that maximize independence and opportunities for older people to participate and contribute as equal, active citizens. Services will be attuned to the needs and wishes of individuals and communities and will actively promote equality."¹⁷⁰

5.3.6 Disability/Quality of Life

Putting People First (DoH, 2007)¹⁶⁹ is underpinned by a set of values that includes "ensuring older people, people with chronic conditions, disabled people and people with mental health problems have the best possible quality of life and the equality of independent living". The relationship between required levels of service support (and hence associated costs) and severity in AD is complex. Such a link needs to take account of the greater number of other disabilities and comorbidities suffered by patients with severe AD. These interactions complicate the interpretation of cost and outcome data related to the severity of AD. In such circumstances it is important that any economic model considering memantine is based on highly conservative assumptions.

Whilst memantine can improve the quality of life of AD patients in terms of clinical benefits, this can have an indirect effect on the quality of life of carers. Particularly in informal care settings, carers are often spouses or partners who are likely to be advanced in age and with health concerns of their own. This is also an important issue as highlighted in the *Carers at the heart in the 21st century* document (DoH, 2008).¹⁷³ The document states that "every carer should be supported so that caring does not adversely affect their health" and as such it is important "that both carers and the people they care for are given as much choice and control as possible when accessing NHS services".

5.4 Conclusions

5.4.1 Why AD in General Deserves Special Consideration

Alzheimer's is a debilitating disease whose progressive nature causes a distinct loss of independence, thereby placing increased burden on carers and health care resource use which translates into high financial costs. In addition, costs to the patient are high in terms of personal safety, in that elderly people with dementia are often at risk of age discrimination with regards to treatment, abuse or mistreatment, and diminished quality of life. Moreover, the lack of understanding and awareness in the professional setting can lead to under-diagnosis and therefore a severe unmet medical need. Alongside placing a large financial burden on society, this directly violates the concept of beneficence, which involves an obligation to benefit individuals to the extent such a benefit is possible. In order to avoid age discrimination, respect the autonomy of dementia patients and adhere to the concept of patient-centred care, personalised care packages providing the best possible care are called for which deliver appropriate intervention.

5.4.2 Why Memantine Deserves Special Consideration

Although there is still a call for a higher standard care in all patients with dementia, this is especially true for patients in moderate to severe stages of Alzheimer's in whom the clinical need is most severe, and yet

is significantly unmet. Memantine specifically targets this population which allows for a lower service impact, greater net benefit, and cost containment with regards to resource use and carer burden. These benefits exist for both the public and private sector, as memantine can allow for reduced need in the level of global care. Moreover, memantine improves behavioural symptoms and quality of life for patients and carers, allowing the retention of independence. The benefits of memantine are significant and widespread, yet memantine makes few additional demands on NHS resources, as use of this drug would simply represent recognition that the disease state of a patient has become more severe.

6.0 REFERENCES

1. Boller F, Verny M, Hugonot-Diener L, et al. Clinical features and assessment of severe dementia. A review. *Eur J Neurol* 2002 Mar;9(2):125-36
2. Bullock R, Hammond G. Realistic expectations: the management of severe Alzheimer disease. *Alzheimer Dis Assoc Disord* 2003 Jul-Sep;17 Suppl 3:S80-5
3. Hogan DB, Bailey P, Black S, et al. Diagnosis and treatment of dementia: 4. Approach to management of mild to moderate dementia. *CMAJ* 2008;179(8):787-93
4. Herrmann N, Gauthier S. Diagnosis and treatment of dementia: 6. Management of severe Alzheimer disease. *CMAJ* 2008 Dec 2;179(12):1279-87
5. Scarmeas N, Brandt J, Blacker D, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol* 2007 Dec;64(12):1755-61
6. Ballard C, O'Brien J, Gray A, et al. Attention and fluctuating attention in patients with dementia with Lewy bodies and Alzheimer disease. *Arch Neurol* 2001 Jun;58(6):977-82
7. Desai AK, Grossberg GT, Sheth DN. Activities of daily living in patients with dementia: clinical relevance, methods of assessment and effects of treatment. *CNS Drugs* 2004;18(13):853-75
8. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 1997 May;48(5 Suppl 6):S10-6
9. Mendez MF, Martin RJ, Smyth KA, et al. Disturbances of person identification in Alzheimer's disease. A retrospective study. *J Nerv Ment Dis* 1992 Feb;180(2):94-6
10. Nyatsanza S, Shetty T, Gregory C, et al. A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2003 Oct;74(10):1398-402
11. Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. *Br J Psychiatry* 1990 Jul;157:86-94
12. Ryu SH, Katona C, Rive B, et al. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. *Am J Geriatr Psychiatry* 2005 Nov;13(11):976-83
13. Aalten P, de Vugt ME, Jaspers N, et al. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005 Jun;20(6):523-30
14. Bullock R. The needs of the caregiver in the long-term treatment of Alzheimer disease. *Alzheimer Dis Assoc Disord* 2004 Apr-Jun;18 Suppl 1:S17-23
15. Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer's disease. *Int Psychogeriatr* 2010 Jan 25:1-27
16. Bassiony MM, Lyketsos CG. Delusions and hallucinations in Alzheimer's disease: review of the brain decade. *Psychosomatics* 2003 Sep-Oct;44(5):388-401
17. Devanand DP, Jacobs DM, Tang MX, et al. The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry* 1997 Mar;54(3):257-63
18. Devanand DP. Behavioral complications and their treatment in Alzheimer's disease. *Geriatrics* 1997 Sep;52 Suppl 2:S37-9
19. Senanarong V, Jamjumras P, Harmphadungkit K, et al. A counseling intervention for caregivers: effect on neuropsychiatric symptoms. *Int J Geriatr Psychiatry* 2004 Aug;19(8):781-8
20. Mega MS, Cummings JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 1996 Jan;46(1):130-5

21. Murman DL, Chen Q, Powell MC, et al. The incremental direct costs associated with behavioral symptoms in AD. *Neurology* 2002 Dec 10;59(11):1721-9
22. Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* 2005 Oct;62(10):1601-8
23. Lopez OL, Becker JT, Brenner RP, et al. Alzheimer's disease with delusions and hallucinations: neuropsychological and electroencephalographic correlates. *Neurology* 1991 Jun;41(6):906-12
24. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol Psychiatry* 1989 Jan;25(1):39-48
25. Lopez OL, Brenner RP, Becker JT, et al. EEG spectral abnormalities and psychosis as predictors of cognitive and functional decline in probable Alzheimer's disease. *Neurology* 1997 Jun;48(6):1521-5
26. Holtzer R, Tang MX, Devanand DP, et al. Psychopathological features in Alzheimer's disease: course and relationship with cognitive status. *J Am Geriatr Soc* 2003 Jul;51(7):953-60
27. Holtzer R, Wegesin DJ, Albert SM, et al. The rate of cognitive decline and risk of reaching clinical milestones in Alzheimer disease. *Arch Neurol* 2003;60(8):1137-42
28. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002 Apr 24;287(16):2090-7
29. Magni E, Binetti G, Bianchetti A, et al. Risk of mortality and institutionalization in demented patients with delusions. *J Geriatr Psychiatry Neurol* 1996 Jul;9(3):123-6
30. Husereau D, Wolfson C, Shukla VK. Drug treatments for Alzheimer's disease: efficacy, outcome measurements and cost-effectiveness. Technology overview no 4. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2001
31. Folstein M, Folstein SE, McHugh PR. Key papers in geriatric psychiatry. Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Int J Geriatr Psychiatry* 1998 May;13(5):285-94
32. Schmitt FA, Ashford W, Ernesto C, et al. The severe impairment battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S51-6
33. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S33-9
34. Galasko D, Schmitt F, Thomas R, et al. Detailed assessment of activities of daily living in moderate to severe Alzheimer's disease. *J Int Neuropsychol Soc* 2005 Jul;11(4):446-53
35. Lyketsos CG, Sheppard JM, Steinberg M, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *Int J Geriatr Psychiatry* 2001 Nov;16(11):1043-53
36. Katona C, Livingston G, Cooper C, et al. International Psychogeriatric Association consensus statement on defining and measuring treatment benefits in dementia. *Int Psychogeriatr* 2007 Jun;19(3):345-54
37. Knopman DS, Knapp MJ, Gracon SI, et al. The Clinician Interview-Based Impression (CIBI): a clinician's global change rating scale in Alzheimer's disease. *Neurology* 1994 Dec;44(12):2315-21
38. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S22-32
39. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005 Dec 17;366(9503):2112-7

40. NICE Guideline: National Collaborating Center for Mental Health commissioned by the Social Care Institute for Excellence, National Institute for Health and Clinical Excellence. A NICE–SCIE Guideline on supporting people with dementia and their carers in health and social care. National Clinical Practice Guideline Number 42. National Collaborating Center for Mental Health: The British Psychological Society & The Royal College of Psychiatrists; 2007
41. Dementia 2010: The prevalence, economic cost and research funding of dementia compared with other major diseases: The Alzheimer's Research Trust; University of Oxford, January 2010,
42. NICE technology appraisal guidance 111: Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease. National Institute for Health and Clinical Excellence; November 2006 (amended September 2007)
43. Copeland JR, McCracken CF, Dewey ME, et al. Undifferentiated dementia, Alzheimer's disease and vascular dementia: age- and gender-related incidence in Liverpool. The MRC-ALPHA Study. *Br J Psychiatry* 1999 Nov;175:433-8
44. Mercy L, Hodges JR, Dawson K, et al. Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology* 2008 Nov 4;71(19):1496-9
45. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003 Aug;60(8):1119-22
46. Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. *Am J Psychiatry* 1989 May;146(5):577-87
47. Paulsen JS, Ready RE, Stout JC, et al. Neurobehaviors and psychotic symptoms in Alzheimer's disease. *J Int Neuropsychol Soc* 2000 Nov;6(7):815-20
48. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry* 2005 Nov;162(11):2022-30
49. Rao V, Lyketsos CG. Delusions in Alzheimer's disease: a review. *J Neuropsychiatry Clin Neurosci* 1998;10(4):373-82
50. Burns A, Folstein S, Brandt J, et al. Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *J Nerv Ment Dis* 1990 Jan;178(1):20-6
51. Burns A, O'Brien J. Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *Journal of Psychopharmacology* 2006;20(6):732-55
52. Burns A, Jacoby R, Levy R. Behavioral abnormalities and psychiatric symptoms in Alzheimer's disease: preliminary findings. *Int Psychogeriatr* 1990 Spring;2(1):25-36
53. Wimo A, Jonsson L, Winblad B. An estimate of the worldwide prevalence and direct costs of dementia in 2003. *Dement Geriatr Cogn Disord* 2006;21(3):175-81
54. Lowin A, Knapp M, McCrone P. Alzheimer's disease in the UK: comparative evidence on cost of illness and volume of health services research funding. *Int J Geriatr Psychiatry* 2001 Dec;16(12):1143-8
55. Parks SM, Novielli KD. A practical guide to caring for caregivers. *Am Fam Physician* 2000 Dec 15;62(12):2613-22
56. Chang HY, Chiou CJ, Chen NS. Impact of mental health and caregiver burden on family caregivers' physical health. *Arch Gerontol Geriatr* 2009 May 12
57. Razani J, Kakos B, Orieta-Barbalace C, et al. Predicting caregiver burden from daily functional abilities of patients with mild dementia. *J Am Geriatr Soc* 2007 Sep;55(9):1415-20
58. Orgogozo J-M, Gauthier S. Alzheimer's disease behavioural symptoms increase resource utilization. 11th International Conference on Alzheimer's Disease; 2008; Chicago, IL, USA. 2008.

59. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int J Geriatr Psychiatry* 2008 May;23(5):537-45
60. Gaugler JE, Yu F, Krichbaum K, et al. Predictors of nursing home admission for persons with dementia. *Med Care* 2009 Feb;47(2):191-8
61. Kesselring A, Krulik T, Bichsel M, et al. Emotional and physical demands on caregivers in home care to the elderly in Switzerland and their relationship to nursing home admission. *Eur J Public Health* 2001 Sep;11(3):267-73
62. Livingston G, Katona C, Roch B, et al. A dependency model for patients with Alzheimer's disease: its validation and relationship to the costs of care--the LASER-AD Study. *Curr Med Res Opin* 2004 Jul;20(7):1007-16
63. Winblad B, Brodaty H, Gauthier S, et al. Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success? *Int J Geriatr Psychiatry* 2001 Jul;16(7):653-66
64. Geldmacher DS, Frolich L, Doody RS, et al. Realistic expectations for treatment success in Alzheimer's disease. *J Nutr Health Aging* 2006 Sep-Oct;10(5):417-29
65. Livingston G, Katona C. The place of memantine in the treatment of Alzheimer's disease: a number needed to treat analysis. *Int J Geriatr Psychiatry* 2004 Oct;19(10):919-25
66. Hansen RA, Gartlehner G, Webb AP, et al. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging* 2008;3(2):211-25
67. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006(1):CD005593
68. Gauthier S, Feldman H, Hecker J, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatr* 2002 Dec;14(4):389-404
69. Gauthier S, Feldman H, Hecker J, et al. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. *Curr Med Res Opin* 2002;18(6):347-54
70. Howard RJ, Juszcak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med* 2007 Oct 4;357(14):1382-92
71. Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. *Arch Intern Med* 2009 May 11;169(9):867-73
72. Winblad B, Jones RW, Wirth Y, et al. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. *Dement Geriatr Cogn Disord* 2007;24(1):20-7
73. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev* 2006(2):CD003154
74. Wilkinson D, Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;24(2):138-45
75. Ballard CG, Waite J, Birks J. Atypical antipsychotics for aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006. Issue 1. Art. No.: CD003476. DOI: 10.1002/14651858.CD003476.pub2.
76. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005 Oct 19;294(15):1934-43
77. Jones RW. A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. *Int J Geriatr Psychiatry* 2010 Jan 4

78. European Medicines Evaluation Agency (EMA). EMA Public statement on the safety of olanzapine (Zyprexa, Zyprexa Velotab). Doc. Ref. EMA/CPMP/856/04/Final; 2004
79. Food, Drug Administration. FDA Alert [4/11/2005]: Increased Mortality in Patients with Dementia-Related Psychosis. [cited 26 February 2010]; Available from: <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/UCM053171>.
80. Medicines and Regulatory Healthcare products Agency (MHRA). New Advice issued on risperidone and olanzapine. Press Release, 2004.
81. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006 Mar;14(3):191-210
82. Ballard C, Margallo-Lana M, Juszcak E, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ* 2005 Apr 16;330(7496):874
83. Banerjee S, Willis R, Matthews D, et al. Improving the quality of care for mild to moderate dementia: an evaluation of the Croydon Memory Service Model. *Int J Geriatr Psychiatry* 2007;22:782-8
84. Rabins PV, Blacker D, Rovner BW. Practice Guideline for the Treatment of Patients with Alzheimer's disease and Other Dementias. 2nd Edition ed.; 2007
85. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline; 2006
86. Wilcock GK, Ballard CG, Cooper JA, et al. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry* 2008 Mar;69(3):341-8
87. National Institute of Health & Clinical Excellence (NICE). National Institute for Health and Clinical Excellence - Donepezil, rivastigmine, galantamine and memantine for the treatment of Alzheimer's disease Appeal by Lundbeck Limited; 2006
88. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry* 2000;57(10):968-76
89. European Agency for the Evaluation of Medicinal Products. Guideline on medicinal products for the treatment of Alzheimer's Disease and other dementias. 2008 [updated 2008; cited]; Available from: <http://www.ema.europa.eu/pdfs/human/ewp/055395en.pdf>.
90. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 2003 Apr 3;348(14):1333-41
91. van Dyck CH, Tariot PN, Meyers B, et al. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. *Alzheimer Dis Assoc Disord* 2007 Apr-Jun;21(2):136-43
92. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004 Jan 21;291(3):317-24
93. Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. *J Alzheimers Dis* 2008 Feb;13(1):97-107
94. Peskind ER, Potkin SG, Pomara N, et al. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. *Am J Geriatr Psychiatry* 2006 Aug;14(8):704-15

95. Porsteinsson AP, Grossberg GT, Mintzer J, et al. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res* 2008 Feb;5(1):83-9
96. Cummings JL. Alzheimer's disease. *N Engl J Med* 2004 Jul 1;351(1):56-67
97. Emre M, Mecocci P, Stender K. Pooled analyses on cognitive effects of memantine in patients with moderate to severe Alzheimer's disease. *J Alzheimers Dis* 2008 Jun;14(2):193-9
98. Hansen RA, Gartlehner G, Lohr KN, et al. Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. *Drugs Aging* 2007;24(2):155-67
99. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. *Biol Psychiatry* 2006 Jun 1;59(11):990-6
100. Modrego PJ, Fayed N, Errea JM, et al. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. *Eur J Neurol* 2009 Oct 28
101. Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol* 2009 Feb;8(2):151-7
102. Calabrese P, Essner U, Forstl H. Memantine (Ebixa) in clinical practice - results of an observational study. *Dement Geriatr Cogn Disord* 2007;24(2):111-7
103. Stamouli S, Tzanakaki M, Laggis N, et al. Effects of memantine on instrumental activities of daily living in a large Greek observational study. 9th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD); 2009; Prague, Czech Republic. 2009.
104. Georgescu R, Vincent Q. Memantine in patients with Alzheimer's disease: results of an observational study in Romania. 13th Congress of the European Federation of Neurological Societies; 2009; Florence, Italy. 2009.
105. Rainer M, Wuschitz A, Jagsch C, et al. Memantine in everyday medical practice: beneficial effects in moderate to severe alzheimer's: Alzheimer's diseaseP2084. 9th Congress of the European Federation of Neurological Societies; 2005; Athens, Greece. 2005.
106. Fröhlich L, Hartmann S, Lambert-Baumann J, et al. Memantine in Alzheimer's disease – results of an observational study. 13th Congress of the European Federation of Neurological Societies; 2009; Florence, Italy. 2009.
107. Gdovinova Z, Safarik P. Memantin (uncompetitive NMDA receptors antagonist) in clinical practice.
108. Riepe MW, Hartman S, Lambert-Bauman J, et al. Memantine in the treatment of nursing home patients with Alzheimer's disease. 13th congress of the European federation of neurological societies EFNS; 2009; Florence, Italy. 2009.
109. Riepe MW, Hartman S, Lambert-Bauman J, et al. Memantine in Alzheimer's disease- Result of an observational study in nursing home patients. Alzheimer's association international conference on Alzheimer's disease; 2009; Vienna, Austria. 2009.
110. Paraskevi S, Triantafyllos D, Panayiotis I, et al. Beneficial Effects of Memantine in a Monotherapy Observational Study in Greece. 13th Congress of the European Federation of Neurological Societies (EFNS); 2009; Florence, Italy. P2101. 2009.
111. Hartmann S, Mobius HJ. Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy. *Int Clin Psychopharmacol* 2003 Mar;18(2):81-5
112. Vidal JS, Lacombe JM, Dartigues JF, et al. Evaluation of the impact of memantine treatment initiation on psychotropics use: a study from the French national health care database. *Neuroepidemiology* 2008;31(3):193-200

113. Lopez OL, Becker JT, Wahed AS, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry* 2009 Jun;80(6):600-7
114. Atri A, Shaughnessy LW, Locascio JJ, et al. Long-term course and effectiveness of combination therapy in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2008 Jul-Sep;22(3):209-21
115. Martinez Rivera M, Menéndez M, Calatayud MT. Psychiatric symptoms and carer distress in patients with moderate to severe Alzheimer's disease treated with memantine. 12th Congress of the European Federation of Neurological Societies; 2008; Madrid, Spain. 2008.
116. Clerici F, Vanacore N, Elia A, et al. Memantine in moderately-severe-to-severe Alzheimer's disease: a postmarketing surveillance study. *Drugs Aging* 2009;26(4):321-32
117. Fillit H, Hofbauer RK, Setyawan J, et al. Memantine Discontinuation in Nursing Home Residents With Alzheimer's Disease is Associated With Increased Psychotropic Drug Use and Decreased Weight. *Academy of Managed Care Pharmacy 20th Annual Meeting and Showcase*; 2008; San Francisco, CA. 2008.
118. Fillit H, Hofbauer RK, Setyawan J, et al., editors. Memantine Discontinuation in Nursing Home Residents With Alzheimer's Disease is Associated With an Increase in Alzheimer's Disease Symptoms. 12th Annual Congress of the European Federation of Neurological Societies; 2008; Madrid, Spain.
119. Periodic Safety Update Report (PSUR 2009) Internal document.
120. European Medicines Evaluation Agency (EMA). Ebixa Procedure number : EMEA/H/C/463/II/15, 15 November 2005. 2006 [updated 2006; cited 29 January 2010]; Available from: <http://www.ema.europa.eu/humandocs/PDFs/EPAR/ebixa/Ebixa-H-463-II-15-SD.pdf>
121. Farlow MR, Graham SM, Alva G. Memantine for the treatment of Alzheimer's disease: tolerability and safety data from clinical trials. *Drug Saf* 2008;31(7):577-85
122. European Agency for the Evaluation of Medicinal Products. European Public Assessment Report (EPAR) for Memantine (EMA/H/C/463/II/15). London, UK: EMA; 2005
123. Thomas SJ, Grossberg GT. Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clin Interv Aging* 2009;4:367-77
124. Stern Y, Tang MX, Albert MS, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* 1997 Mar 12;277(10):806-12
125. Caro JJ, Getsios D, Migliaccio-Walle K, et al. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. *Neurology* 2001 Sep 25;57(6):964-71
126. Getsios D, Caro JJ, Caro G, et al. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. *Neurology* 2001 Sep 25;57(6):972-8
127. Green C. Modelling disease progression in Alzheimer's disease: a review of modelling methods used for cost-effectiveness analysis. *Pharmacoeconomics* 2007;25(9):735-50
128. Bonsignore M, Heun R. Mortality in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2003;15(4):231-6
129. Max W, Webber P, Fox P. Alzheimer's disease. The unpaid burden of caring. *J Aging Health* 1995 May;7(2):179-99
130. National Institute for Clinical Excellence (NICE). Incorporating health economics in guidelines and assessing resource impact. London: Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers. Guide to the Methods of Technology Appraisals, June 2008. . 2004 [updated 2004; cited]; Available from: <http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf>.

131. Green C, Picot J, Loveman E, et al. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. *Pharmacoeconomics* 2005;23(12):1271-82
132. Kronborg AC, Søgaard J, Hansen E, et al. The Cost of Dementia in Denmark: The Odense Study Dementia and Geriatric Cognitive Disorders 1999;10(4)
133. Wolstenholme J, Fenn P, Gray A, et al. Estimating the relationship between disease progression and cost of care in dementia. *Br J Psychiatry* 2002 Jul;181:36-42
134. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984 Nov;141(11):1356-64
135. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994 Dec;44(12):2308-14
136. Radosevitch DM, Pruitt M. Twelve-item health status questionnaire (HSQ-12) cooperative validation project: comparability study. AHSR FHSR Annual Meeting; 1996. 1996.
137. Ferm L. Behavioural activities in demented geriatric patients. Study based on evaluations made by nursing staff members and on patients' scores on a simple psychometric test. *Gerontol Clin (Basel)* 1974;16(4):185-94
138. Logsdon RG, Gibbons LE, McCurry SM, et al. Quality of life in Alzheimer's disease: patient and carer reports. *J Ment Health Ageing* 1999;5:21-32
139. Sapin C, Livingston G, Katona C, et al. Main factors influencing preference-based utility values in Alzheimer's disease: Results from the LASER-AD Study. 7th International Conference on Alzheimer's and Parkinson's Disease (AD/PD); 2005; Sorrento, Italy. 2005.
140. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997 Nov;35(11):1095-108
141. Beecham J, Knapp MRJ. Costing psychiatric intervention. In: Thornicroft GJ, Brewin CR, Wing JK, editors. *Measuring mental health needs*. London: Gaskell; 1992.
142. Curtis L. Unit Costs of Health and Social Care 2009, Personal Social Services Research Unit. 2009; Canterbury. University of Kent; 2009.
143. Loveman E, Green C, Kirby J, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. *Health Technol Assess* 2006 Jan;10(1):iii-iv, ix-xi, 1-160
144. BNF. British National Formulary (BNF) 58. British National Formulary (BNF) website. 2010 [updated 2010; cited 16th Jan 2010]; Available from: <http://www.bnf.org/bnf/>.
145. National Institute of Health & Clinical Excellence (NICE). Guide to the methods of technology appraisal. National Institute of Health & Clinical Excellence (NICE) website. 2008 [updated 2008; cited Feb 2010]; Available from: <http://www.nice.org.uk/>.
146. Kurz X, Scuvee-Moreau J, Rive B, et al. A new approach to the qualitative evaluation of functional disability in dementia. *Int J Geriatr Psychiatry* 2003 Nov;18(11):1050-5
147. Andersen CK, Wittrup-Jensen KU, Lolk A, et al. Ability to perform activities of daily living is the main factor affecting quality of life in patients with dementia. *Health and Quality of Life Outcomes* 2004;2:52
148. Ward A, Caro JJ, Getsios D, et al. Assessment of health economics in Alzheimer's disease (AHEAD): treatment with galantamine in the UK. *Int J Geriatr Psychiatry* 2003 Aug;18(8):740-7
149. Neumann PJ. Lundbeck response to the SHTAC Assessment Group report. Appendix 5. Estimates of Health Utilities by Level of Dependency in Alzheimer's Disease. 4th October, 2004
150. Kavanagh S, Schneider J, Knapp M, et al. Elderly people with cognitive impairment: Costing possible changes in the balance of care. *Health Soc Care Commun* 1993;1:69-80

151. Ferris SH, Schmidt F, Doody R. Long-term treatment with the NMDA antagonist, memantine: results of a 24-week, open-label extension study in advanced Alzheimer's disease. Annual Meeting of the American College of Neuropsychopharmacology; 2001; Waikoloa Village, Hawaii, USA. 2001.
152. Jones RW, McCrone P, Guillaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. *Drugs Aging* 2004;21(9):607-20
153. Francois C, Sintonen H, Sulkava R, et al. Cost effectiveness of memantine in moderately severe to severe Alzheimer's disease : a markov model in Finland. *Clin Drug Investig* 2004;24(7):373-84
154. Jonsson L. Cost-effectiveness of memantine for moderate to severe Alzheimer's disease in Sweden. *Am J Geriatr Pharmacother* 2005 Jun;3(2):77-86
155. Antonanzas F, Rive B, Badenas JM, et al. Cost-effectiveness of memantine in community-based Alzheimer's disease patients: An adaptation in Spain. *Eur J Health Econ* 2006 Jun;7(2):137-44
156. Gagnon M, Rive B, Hux M, et al. Cost-effectiveness of memantine compared with standard care in moderate-to-severe Alzheimer disease in Canada. *Can J Psychiatry* 2007 Aug;52(8):519-26
157. Caro J, Getsios D, Migliaccio-Walle K, et al. Rational choice of cholinesterase inhibitor for the treatment of Alzheimer's disease in Canada: a comparative economic analysis. *BMC Geriatr* 2003 Dec 15;3:6
158. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making* 2003 Jul-Aug;23(4):341-50
159. Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. *Curr Med Res Opin* 2007 May;23(5):1187-97
160. Wimo A, Winblad B, Stoffler A, et al. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics* 2003;21(5):327-40
161. Office of National Statistics: Projected populations at mid-years by age last birthday, England & Wales, 2008-based. [cited 01/02/2010]; Available from: http://www.statistics.gov.uk/downloads/theme_population/NPP2008/wEW08singyear.xls.
162. Haw C, Stubbs J, Yorston G. Antipsychotics for BPSD: an audit of prescribing practice in a specialist psychiatric inpatient unit. *Int Psychogeriatr* 2008 Aug;20(4):790-9
163. All Party Parliamentary Group on Dementia: Always a last resort, April 2008. [cited 26 Feb 2010]; Available from: <http://www.alzheimers.org.uk/site/scripts/download.php?fileID=322>.
164. Ballard C, Lana MM, Theodoulou M, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). *PLoS Med* 2008 Apr 1;5(4):e76
165. NICE implementation uptake report: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease; May 2009
166. National Institute for Health and Clinical Excellence. Social Value Judgements: Principles for the development of NICE guidance, 2nd edition. 2008
167. Department of Health. National service framework for older people. London: DoH; 2001
168. Department of Health. Living well with dementia; a national dementia strategy. London: DoH; 2009
169. Department of Health. Putting People First: A shared vision and commitment to the transformation of Adult Social Care. London: DoH; 2007
170. Department of Health. New Horizons: Towards a shared vision for mental health. London: DoH; 2009

171. Knapp M. Economic outcomes and levers: impacts for individuals and society. *Int Psychogeriatr* 2007 Jun;19(3):483-95
172. Horgas AL, Tsai PF. Analgesic drug prescription and use in cognitively impaired nursing home residents. *Nurs Res* 1998 Jul-Aug;47(4):235-42
173. Department of Health. *Carers at the heart of 21st century families and communities: A caring system on your side, A life of your own*. London: DoH; 2008