ARICEPT® (DONEPEZIL)

SUBMISSION TO THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL (MTA)

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EXECUTIVE SUMMARY

Submission Overview and Recommendations

- Alzheimer's disease (AD) is a serious progressive neurodegenerative disorder with devastating consequences for the patient. There will be a significant rise in the number of sufferers and a consequent escalation in the costs to the NHS and Personal Social Services of providing care for these patients in England and Wales. It is imperative that effective therapies are made available to minimise the burden to the individual patient, their carers and society from the earliest symptomatic stages of the disease.
- There is a significant body of evidence, previously accepted by NICE and restated here, that demonstrates the efficacy of donepezil in the symptomatic management of both mild and moderate AD. This evidence base shows that donepezil delays symptomatic deterioration in a number of aspects of the disease, including cognition, behavioural symptoms and function, and that cessation of therapy results in a rapid loss of these benefits.
- Health economic modelling techniques based on longer term efficacy data and capable of capturing multiple dimensions of efficacy (behavioural, function and cognition) demonstrate donepezil is cost effective in both mild and moderate AD patients. Donepezil is estimated to result in savings in the costs of institutionalisation that outweigh its acquisition costs. The size of the health benefits and savings associated with donepezil are greater in patients with mild AD compared to those with moderate symptoms of the disease.
- AChEIs and memantine are the only pharmacological treatments available to treat the symptoms of AD. Donepezil should be recommended by NICE for the treatment of both mild and moderate AD based on both clinical and cost effectiveness grounds. A recommendation encouraging active therapeutic management from the earliest symptomatic stages of disease will be a major element in achieving the aims of the National Dementia Strategy.

1. ISSUES IN THE MANAGEMENT OF ALZHEIMER'S DISEASE IN THE UK TODAY

- AD is a neurodegenerative disorder whose natural course is one of progressive deterioration in the domains of cognition, function and behaviour. The symptoms of this ultimately fatal disease progress from mild through moderate to severe. Given the multifaceted nature of AD no single assessment tool can be used to assess efficacy or the success of treatment strategies.

- There are more than 820,000 people with dementia living in the UK, of whom approximately 60% (490,000) are estimated to have AD. The number of people with AD is expected to increase to approximately 1.7 million by 2051.
- Dementia is estimated to have cost the UK economy £23 billion in 2008. This is projected to rise to £34.8 billion by 2026. Of the total, long-term care costs are estimated to account for 40% and informal care (opportunity costs of unpaid care), for 55% of the total. Licensed anti-dementia drug costs account for less than one per cent of the total cost.
- Donepezil hydrochloride is an acetylcholinesterase inhibitor (AChEI) indicated for the symptomatic treatment of mild to moderately severe AD. Donepezil was licensed in 1997 and available in over 90 countries worldwide and has been used for over 5.6 billion days of patient treatment. There is abundant clinical evidence that donepezil is effective in the symptomatic treatment of mild to moderate AD. Its license states that treatment should be continued for as long as a therapeutic benefit for the patient exists.
- The National Institute for Heath and Clinical Excellence (NICE) currently recommends the use of three AChEIs, donepezil, rivastigmine and galantamine, as one component of the management of people with moderate AD only, where moderate is defined by NICE in its guidance as a Mini Mental State Examination (MMSE) score of 10–20 points.
- In February 2009, the government published its first ever national dementia strategy *(Living Well with Dementia: A National Dementia Strategy*) which aims to ensure that significant improvements are made to dementia services across three key areas: improved awareness, earlier diagnosis and intervention, and a higher quality of care.
- Currently only 49% of people in the UK with dementia receive a formal diagnosis. Reasons include a lack of public awareness and stigma, and a lack of knowledge, expertise and confidence among general practitioners (GPs) in recognising symptoms and referring for a specialist diagnosis.
- In those AD patients diagnosed, the *National Dementia Strategy* highlights the fact that anti-psychotics are being prescribed inappropriately. More money is spent on anti-psychotic drugs for AD patients (£128 million) in the UK than on the 4 anti-dementia drugs (£100 million).
- The NICE recommendations regarding the therapeutic management of AD should complement and support the National Dementia Strategy to encourage positive and active management of AD from its earliest symptomatic stages.

2. CLINICAL EFFECTIVENESS OF DONEPEZIL

- Donepezil has been investigated in a large number of clinical trials and observational studies. Presented here is the trial evidence published since 2004 and a summary of trials

from the previous two submissions. In all, 12 placebo-controlled RCTs, three head-to-head RCTs and six meta-analyses of trial data are presented. In addition, non-RCT evidence published since 2004 is presented consisting of two prospective longitudinal studies, and 3 observational studies

- A pooled meta-analysis of patient level data from 11 trials confirmed significant benefits in cognition for patients with mild AD treated with donepezil compared to placebo.
- Another pooled meta-analysis of ten trials showed that donepezil led to a significant improvement in global function compared with placebo in both mild and moderate AD. This analysis also showed a greater benefit from donepezil treatment may be observed in mild rather than moderate disease and that earlier treatment may be associated with greater preservation of function.
- All 12 placebo-controlled RCTs report on the domain of cognition and all found a significant advantage for donepezil versus placebo.
- Of seven RCTs reporting on the function domain, four reported a statistically significant difference favouring donepezil versus placebo on at least one scale, while the other three reported non-significant trends in favour of donepezil. In addition, a recently published meta-analysis of seven donepezil RCTs found a statistically significant advantage favouring donepezil versus placebo on the function domain.
- Of seven RCTs investigating the effects of donepezil on the behavioural symptoms of AD, three found a significant difference between donepezil and placebo on the Neuropsychiatric Inventory (NPI) score. In addition, a recently published meta-analysis of donepezil RCTs found a statistically significant difference in favour of donepezil compared with placebo on the NPI total score.
- Two RCTs and one observational study demonstrate that improvements in neuropsychiatric symptoms that are produced by donepezil are accompanied by a reduction in levels of caregiver stress and burden. In a sub-analysis of a one-year RCT, time spent caring for patients with AD was approximately one hour per day less for the caregivers of patients who received donepezil compared with those who received placebo.
- Two prospective longitudinal studies in patients with mild to moderate AD show that the beneficial effects of donepezil on cognition and function are maintained for at least 3 years. Two RCTs and one prospective longitudinal study also demonstrate that the benefits of donepezil treatment are lost rapidly upon cessation of treatment and (particularly neuropsychiatric) symptoms re-emerge.
- One RCT found that an initial decline or stabilisation in MMSE score is not necessarily indicative of a lack of treatment effect. Discontinuation of treatment should therefore be based on specialist assessment of the individual patient and must not be based a single assessment parameter such as crude MMSE score.

- One double-blind head-to-head RCT and a Cochrane review indicated that the magnitude of clinical effect is similar across the AChEI class, but a more favourable tolerability profile for donepezil compared with the other AChEIs has been observed.
- A double-blind, placebo-controlled RCT demonstrates that continued donepezil therapy with the addition of memantine is a beneficial treatment strategy.
- Given the evidence that patients with mild AD experience cognitive and functional benefit from donepezil, treatment should be initiated as early in the disease as possible to delay symptomatic progression and realise optimal clinical benefit.

3. COST-EFFECTIVENESS OF DONEPEZIL

- A literature search designed to identify economic studies published since 2004, found four cost effectiveness studies relevant for the UK. These studies had the following limitations:
    - The efficacy of the AD treatments is often represented by a single scale, usually cognition (e.g. MMSE) which does not capture the full nature of the disease and treatment benefits.
    - Aggregated health states were used which were not able to capture treatment benefits in adequate sufficient detail.
    - Cohort model approaches used did not consider individual characteristics in predicting outcomes, variability in outcomes over the course of the disease or other factors that impact long term outcomes, such as persistence with treatment.
    - They were based on short term (6 months or less) clinical trial evidence.
- A de novo economic model was developed for this submission which uses discrete event simulation to provide a more detailed and accurate estimate of the cost effectiveness of donepezil. This approach is able to capture the individual variability between patients in terms of disease progression, treatment success and mortality. In particular, the model has the following advantages:
- Continuous measurement of health and disease progression on multiple scales (MMSE, NPI, ADL, IADL);
- Multivariate predictors of patient and caregiver utilities based on continuous measures of disease severity and finer gradations of severity in the assignment of costs and nursing home care;
- Incorporates estimates of donepezil efficacy based on multiple long term (up to 12 months) follow up randomised controlled trials;

- Base case analyses based on current list price show that donepezil is cheaper and more effective (dominates) compared with no treatment in both mild and moderate AD patients in the UK in the base case analyses.
- Both QALY gains (mild 0.133 vs. moderate 0.098) and total cost savings (£3,300 vs £1,900) estimated for donepezil are greater in the mild patient group as compared to the moderate patient group.
- In both mild and moderate AD patients, the acquisition cost of donepezil can be offset by reductions in the need for social services, physician visits and institutionalisation that are already evident during the first 1-2 years of treatment.
- Extensive one way sensitivity analyses show that donepezil remains cost effective in both the mild and moderate patient subgroups under almost all plausible changes in model parameters. Donepezil becomes more cost effective than in the base case, if acquisition costs are assumed to fall following the entry of generics post loss of patent exclusivity in 2012.
- Other one-way sensitivity analyses show that donepezil becomes more expensive and more effective only when there are very large reductions in nursing home costs or reductions in overall costs of care specifically for the patients who move into the severe stages of AD. Even in these analyses the cost per Quality Adjusted Life Years (QALYs) are well below the £20,000 threshold (£1,370/QALY and £7,093/QALY respectively) in the moderate AD population. Among patients with AD of mild severity, reducing nursing home costs by 50% resulted in an ICER of £1,866/QALY.
- Probabilistic analyses demonstrate that the probability that the cost effectiveness estimates for donepezil remain below the £20,000 threshold are 74% for the mild AD population and 70% for the moderate population.

4. Wider Implications to the NHS

- AChEIs in general and donepezil in particular are already widely used among patients with mild and moderate AD who are diagnosed and referred to specialist clinics reflecting the value clinicians place upon the value of symptomatic management.
- Compared with current levels of spending, the impact of a recommendation in mild disease for donepezil is estimated to result in an increase in England and Wales of £5.7 million in 2011 and £6.8 million in 2015 in the expenditure on AChEIs.
- However, the additional drug expenditure associated with a mild AD recommendation for donepezil is estimated to be offset by savings resulting from the effect of donepezil in delaying institutionalised care costs. The estimated net budget impact of a donepezil mild AD recommendation is net savings of £1.6 million in 2011 and £4.7 million in 2015 across

England and Wales. Seen another way, if the NICE guidance remains as a recommendation for donepezil in moderate AD patients only, then this will cost the NHS in England and Wales an additional £1.6 to £4.7 million between 2011 and 2015. With a mild AD recommendation for donepezil, costs of institutionalisation are expected to decrease by £8.1 million in 2011 and £12.81 million in 2015 whereas non-institutionalised care costs are expected to increase by £0.84 million in 2011 and £1.32 million in 2015.

- Recommending donepezil for mild AD patients in addition to the current recommendation for moderate AD patients is estimated to result in savings even when key parameters are varied such as rates of patient diagnosis, referral and subsequent treatment. Drug compliance has a limited effect on total cost implications.
- All the above health economic and budget impact calculations are based on the current list price for donepezil which has been reduced by 5.8% since the last guidance. It should be noted however that donepezil will lose patent protection in the UK in February 2012 when several generic versions will become available at a significantly reduced cost (we are aware of a number of generic license approvals to date). Uncertainty concerning the exact generic price post loss of patent should not mean that this fundamental factor is discounted and Eisai/Pfizer are prepared to discuss with NICE guaranteeing a donepezil price post patent expiry in order that the effect of this can be included in health economic modeling approaches.

ABBREVIATIONS AND ACRONYMS

ACDS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADFACS	Alzheimers' Disease Functional Assessment and Change Scale
ADL	Activity of daily living
AE	Adverse event
A & E	Accident and Emergency
AWARE	Aricept Washout and Rechallenge
BADL	Bristol Activities of Daily Living Scale
BD	Twice daily
BDRS	Blessed Dementia Rating Scale
BGP	Behavioural Rating Scale for Geriatric Patients
BPSD	Behavioural and psychological symptoms of dementia
CD	Caregiver diary
CDCIG	Cochrane Dementia and Cognitive Improvement Group
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – sum of boxes
CEAC	Cost effectiveness acceptability curve
CERAD	Consortium to Establish A Registry for Alzheimer's Disease
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
ChEI	Cholinesterase inhibitor
CIBIC	Clinician's Interview-based Impression of Change
CIBIC-Plus	Clinician's Interview Based Impression of Change Plus version
CMAI	Cohen-Mansfield Agitation Inventory
CR	Clinical response
CSS	Caregiver Stress Scale
DAD	Disability Assessment for Dementia
DB	Double-blind
DES	Discrete event simulation
DSM IV	Diagnostic and Statistical Manual, 4th edition
FTC	Full-time care
GBS	Gottfries, Brane and Steen Scale

GDS	Global Deterioration Scale
GHQ	Global Health Questionnaire
GP	General practitioner
HDS-R	Hasegawa Dementia Scale revised
HRQoL	Health related quality of life
IADL	Instrumental activity of daily living
ICD 10	International Classification of Diseases, 10th revision
ICER	Incremental cost-effectiveness ratio
IADL+	Modified Instrumental Activities of Daily Living
IDDD	Interview for Deterioration of Daily Living Activities in Dementia
IDDD-B	Interview for Deterioration of Daily Living Activities in Dementia Basic Task score
IDDD-C	Interview for Deterioration of Daily Living Activities in Dementia Complex Task score
ITT	Intent-to-treat
LOCF	Last observation carried forward
MMSE	Mini Mental State Examination
MSAD	Moderately Severe Alzheimer's Disease study
MRC CFAS	The Medical Research Council Cognitive Function and Ageing Study
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders, Alzheimer's Disease and Related Disorders
NPI	Neuropsychiatric Inventory
NPI-10	Neuropsychiatric Inventory – 10 domains
NPI-12	Neuropsychiatric Inventory- 12 domains
NPI-CDS	Neuropsychiatric Inventory – Caregiver Distress Scale
NPI-NH-10	Neuropsychiatric Inventory – Nursing Home Version- 10 domains
NR	Not reported
NS	Not significant
PCT	Primary Care Trust
PDS	Progressive Deterioration Scale
PSA	Probabilistic sensitivity analysis
PSMS	Physical-Self Maintenance Scale
PSMS+	Modified Physical-Self Maintenance Scale
QALY	Quality-adjusted life year
QOF	Quality and Outcomes Framework
QoL	Quality of life
QoLS	Quality of Life Scale

RCT	Randomised controlled trial
RUD	Resource Utilisation in Dementia
SCIE	Social Care Institute for Excellence
SHTAC	Southampton Health Technology Assessment Centre
SIB	Severe Impairment Battery
S-MMSE	Standardised Mini Mental State Examination
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
UTI	Urinary tract infection

SECTION 1 – BACKGROUND

1.1 Executive Summary

Issues in the Management of Alzheimer's Disease in the UK Today

- AD is a neurodegenerative disorder whose natural course is one of progressive deterioration in the domains of cognition, function and behaviour. The symptoms of this ultimately fatal disease progress from mild through moderate to severe. Given the multifaceted nature of AD no single assessment tool can be used to assess efficacy or the success of treatment strategies.
- There are more than 820,000 people with dementia living in the UK, of whom approximately 60% (490,000) are estimated to have AD. The number of people with AD is expected to increase to approximately 1.7 million by 2051.
- Dementia is estimated to have cost the UK economy £23 billion in 2008. This is projected to rise to £34.8 billion by 2026. Of the total, long-term care costs are estimated to account for 40% and informal care (opportunity costs of unpaid care), for 55% of the total. Licensed anti-dementia drug costs account for less than one per cent of the total cost.
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- The National Institute for Heath and Clinical Excellence (NICE) currently recommends the use of three AChEIs, donepezil, rivastigmine and galantamine, as one component of the management of people with moderate AD only, where moderate is defined by NICE in its guidance as a Mini Mental State Examination (MMSE) score of 10–20 points.
- In February 2009, the government published its first ever national dementia strategy *(Living Well with Dementia: A National Dementia Strategy*) which aims to ensure that significant improvements are made to dementia services across three key areas: improved awareness, earlier diagnosis and intervention, and a higher quality of care.
- Currently only 49% of people in the UK with dementia receive a formal diagnosis. Reasons include a lack of public awareness and stigma, and a lack of knowledge, expertise and confidence among general practitioners (GPs) in recognising symptoms and referring for a specialist diagnosis.
- In those AD patients diagnosed, the *National Dementia Strategy* highlights the fact that anti-psychotics are being prescribed inappropriately. More money is spent on anti-psychotic

drugs for AD patients (£128 million) in the UK than on the 4 anti-dementia drugs (£100 million).

- The NICE recommendations regarding the therapeutic management of AD should complement and support the National Dementia Strategy to encourage positive and active management of AD from its earliest symptomatic stages.

1.2 Introduction

Aricept® (donepezil hydrochloride) is an acetylcholinesterase inhibitor (AChEI) that was licensed in the UK in February 1997 for the symptomatic treatment of mild to moderately severe Alzhiermer's Disease (AD; see the current Summary of Product Characteristics (SmPC) for donepezil which is attached in Appendices A and B). Donepezil is now available in over 90 countries worldwide and has been used for over 5.6 billion days of patient treatment (Eisai Data on File - Extract from Aricept Annual Safety Report 2008-2009). In 2001, the National Institute of Clinical Excellence (NICE) recommended the use of AChEIs in the treatment of patients with mild and moderate AD but in 2006, restricted its recommendation to patients with moderate disease only following a review of the 2001 guidance (subject to additional restrictions ─ see Section 1.7 below). In September 2007 NICE issued amended guidance in which it addressed the use of the Mini Mental State Examination (MMSE) cognitive test in patients with linguistic, learning or communication difficulties. Most recently, in August 2009, a consultation on the economic model used to evaluate the cost effectiveness of donepezil use was held, in response to a judicial review, prompted by Eisai/Pfizer's challenge to the NICE decision. Neither amendment altered the recommendation that donepezil (and rivastigmine and galantamine) should be prescribed to patients in the moderate stages of the disease only.

Eisai Limited and Pfizer Ltd has now been invited by NICE to submit new evidence for donepezil, for a further review of technology appraisal number 111 (TA111) of "Drugs for the Treatment of AD".

This submission focuses on the:

- Clinical evidence for the use of donepezil in the symptomatic treatment of AD since the submission to NICE in 2004.
- Updated cost-effectiveness estimates for the use of donepezil in patients with mild to moderately severe AD.

Based on this evidence this submission recommends that:

- The use of donepezil should be extended to patients with mild AD, helping to attain the goals set out in the government's 2009 *National Dementia Strategy.*
- The assessment of dementia severity on the basis of MMSE alone overly simplifies the disease; decisions concerning patient treatment ─ whether to initiate or continue therapy─ should be based on clinician assessment of individual patient need and response in accordance with the SmPC for donepezil, rather than on crude MMSE criteria alone.

- Thus, patients who initiate treatment in the mild or moderate stages should be able to continue on treatment while the clinician perceives a treatment benefit.

1.3 Issues in the Management of Alzheimer's Disease in the UK Today

1.3.1 What is Alzheimer's Disease?

AD is a progressive and ultimately fatal neurodegenerative disorder whose natural course is one of progressive deterioration in the domains of cognition, function and behaviour (Cummings, 2004).

Although a definitive diagnosis of AD relies upon post-mortem neuropathological assessment, AD can be clinically diagnosed with a high degree of accuracy by experienced clinicians using established diagnostic criteria such as the National Institute of Neurological and Communicative Disorders, Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) (Jenike 1996, McKhann 1984), the Diagnostic and Statistical Manual, 4th edition (DSM IV) (American Psychiatric Association 1994) and the International Classification of Diseases, 10th revision (ICD 10) (World Health Organization,1992).The key elements of a diagnosis of AD are:

- Dementia defined as a loss of memory and cognitive ability sufficiently severe to interfere with past level of function;
- Cognitive decline in two or more domains: memory, language, praxis, visual or spatial processing;
- Continuing progression of cognitive and functional loss;
- Abnormalities in executive function;
- Clear state of consciousness.

Several studies have demonstrated a deficit in the neurotransmitter, acetylcholine (ACh) in AD patients (Davies and Maloney, 1976; Perry et al., 1977; Whitehouse et al., 1981). As a consequence, acetylcholinesterase inhibitors that act to block the acetylcholinesterase (AChE) enzymes that normally hydrolyse ACh have been developed as agents to treat AD.

1.4 The Symptoms of Alzheimer's Disease and their Measurement

1.4.1 Symptoms of AD

AD can be thought of as early, middle or late stage. During the course of the disease symptoms in the domains of cognition, function and behaviour can be mild, moderate or severe.

The symptoms of AD are manifested in the domains of cognition, function and behaviour. Cognitive impairment is identified as deficits in memory, language, orientation and judgement. It is accompanied by progressive functional disability, initially to perform complex tasks and in the later stages to perform the most basic activities of daily living (ADLs). Behavioural symptoms include personality changes, mood disturbances, delusions and hallucinations. Some behavioural disturbances have been linked to the cholinergic deficit that characterizes this disease. Approximately 80% of all AD patients develop behavioural disturbances during the course of their illness (Hart et al., 2003). Although a number of studies have demonstrated a relationship between cognitive and functional losses in AD (Galasko et al., 1997, Boyle et al., 2003), it is not necessarily the case that an individual patient's symptoms in the 3 domains worsen at the same rate. Thus, a patient may manifest mild functional impairment, but more severe cognitive impairment. Thus, a patient's symptoms in all 3 domains of AD must be considered for a full clinical assessment.

Nonetheless, in its early stages, the symptoms of AD in all domains tend to be mild. In the domain of cognition, these include forgetfulness; difficulty with word finding, problem solving or calculation; and errors in judgment. A decline in functional ability, however, is often the first sign that a dementing illness is present. Patients may struggle handling money, cooking, shopping, reading or performing hobbies. Apathy, withdrawal, depression and irritability are common behavioural symptoms in this early stage. However, the AD patient retains many of their capabilities and requires minimal assistance.

With disease progression comes further impairment in recent memory, language, insight, orientation and visuospatial ability. In these middle stages of the disease the patient may have difficulty with tasks such as getting dressed and assistance with many daily tasks will become necessary. Existing behavioural symptoms such as apathy may worsen, while new behavioural disturbances, such as delusions, wandering, agitation and insomnia, may develop.

In the late stages of the disease, the AD patient is often unable to communicate verbally or look after themselves. Assistance with the most basic functions, such as bathing and eating is necessary and care is required 24 hours a day. The clinical course of AD varies considerably;

however, in general patients can be expected to live between 3 and 9 years after diagnosis (Ganguli et al., 2005; Helzner et al., 2008; Larson et al., 2004; Xie et al., 2008).

1.4.2 Measurement of the Severity of AD Symptoms

No single assessment tool can capture the multifaceted aspect of AD progression and therefore decisions as to treatment strategies should not be made on the basis of the outcomes from a single tool. Disease severity and treatment success should be evaluated in terms of a range of parameters that encompass cognitive function, basic and instrumental activities of daily living and behaviour.

A number of assessment tools have been developed to measure disease progression in each of the domains affected by this disease. Each assesses a unique aspect of the global impact of this condition. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog; Rosen et al., 1984) and MMSE (Folstein et al., 1975) are commonly used to assess cognition in clinical practice and as outcome measures in clinical trials of agents for the treatment of AD. However, as recognised by NICE in its 2009 final appraisal decision, MMSE is not always appropriate as a means of assessing the severity of dementia in specific groups of people with AD, such as those with learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties. Additionally, it discriminates against people with high cognitive reserve. Functional status (ability to perform ADLs and more complex instrumental ADLs (IADLs)) and quality of life (QoL) can be captured using the Progressive Deterioration Scale (PDS) while the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) is commonly used to assess the severity of the behavioural and neuropsychiatric symptoms of AD. Global severity scales, which aim to make a comprehensive assessment in the domains of cognition, behaviour, and functioning (Reisberg, 2007), include the Clinical Dementia Rating (CDR) and the related CDR-sum of boxes (CDR-SB); the Global Deterioration Scale (GDS); and the Clinician's Interview-based Impression of Change (CIBIC) and CIBIC-plus. Other surrogate markers of disease progression include measures of caregiver burden, health related quality of life and resource utilisation (Small et al., 1997; Winblad et al., 2001).

Clinical trials necessarily have to rely on assessment tools that are surrogate measures of disease progression and treatment effect. Frequently only one measure is selected as a primary outcome measure and any treatment effects seen on that measure are averages across the study population. Clearly, the approach of using a single outcome measure is not relevant when making treatment decisions that affect an individual patient. In any individual, differing symptom domains are affected to differing extents by disease progression and treatment. In its 2009 final appraisal document, NICE recommended that patients who continue on an AChEI should be reviewed every 6 months by MMSE score *and* global, functional and behavioural assessment. In addition,

carers' views on the patient's condition at follow-up should be sought. Thus, although the MMSE has, historically had precedence over other markers of disease progression, it is important that MMSE not be regarded as the sole determinant in treatment decisions. Instead, a range of tools is essential to provide a clinically meaningful assessment of a patient's disease state.

1.5. Epidemiology of Alzheimer's Disease in the UK

There are more than 820,000 people with dementia living in the UK, of whom approximately 60% (490, 000) are estimated to have AD. The number of people with AD is expected to increase to approximately 1.7 million by 2051.

Incidence and prevalence studies for AD are difficult to conduct, in part due to the challenges involved in diagnosing early stage disease. However, the Alzheimer's Research Trust has estimated that in 2008, there were over 820,000 people with dementia in the UK (Luengo-Fernandez et al., 2010). Of these it is estimated that approximately 60% (490,000) have AD. Among those with late onset dementia, it is estimated that 55.4%, 32.1% and 12.5% are in the early, middle and late stages of the disease, respectively (Knapp et al., 2007).

As the population ages, the number of people with AD is expected to increase. One study has estimated that by 2051 the number of people with dementia in the UK will have increased to 1.7 million (Knapp et al., 2007).

1.6. Mortality and Morbidity Associated with Alzheimer's Disease

Improving the cognitive and behavioural symptoms of AD in its early stages results in more effective, and cost-effective, management of co-morbid conditions in AD patients, at least in part because of improved adherence to therapy for the co-morbid condition.

Co-morbid conditions play a large role in the health of the AD patient. Though these conditions, such as mental health conditions, neurological conditions, cerebrovascular disease and diabetes, are common in older people, individuals with AD are more likely to have co-morbid conditions, and to have more co-morbid conditions than matched nondemented control subjects (Hill et al., 2002a; Kuo et al., 2008) and the prevalence of co-morbid conditions increases with AD severity (Doraiswamy 2002). This is because the cognitive and functional deterioration that characterises AD has a multifaceted impact on the patient's well-being. Thus, appetite and ability to eat may be impaired while alterations in brain function may produce insomnia and irregular sleep patterns. The resultant nutritional deficiencies along with chronic inadequate sleep weaken physical

strength and the immune system, putting the AD patient at increased risk of injury and infection. Because of their cognitive and functional deterioration, AD patients are at great risk for injury because of impaired balance and coordination. As the disease progresses AD patients eventually become bedridden. Pneumonia and skin breakdown are frequent complications of immobility and recovery from injury and illness becomes protracted. Not only do AD patients have more co-morbid conditions than nondemented patients, but their cognitive and functional impairments mean that they are less able to manage their illnesses themselves, thereby compounding the problem. In addition, there is evidence that the presence of co-morbidities contributes to more rapid cognitive decline in these patients (Mielke et al., 2007): conversely, the rate of cognitive decline during the final portion of the preclinical phase of AD (the period before a clinical diagnosis of dementia can be rendered) has been correlated with the number of concomitant health conditions (Bäckman et al., 2003).

Thus, AD not only causes significant disability, but is also associated with reduced life expectancy, with people generally living 3 to 9 years after diagnosis (Ganguli et al., 2005; Helzner et al., 2008; Larson et al., 2004; Xie et al., 2008). Moreover, death from AD is most often secondary to complications that arise from the disease, such as complications of diabetes, heart disease, stroke, kidney failure and other conditions. AD patients often die from conditions such as pneumonia and pulmonary thromboembolism (Fu, 2004). However, as death certificates rarely attribute a cause of death to AD, mortality due to AD is greatly underestimated.

The cost of treating and managing AD patients with co-morbidities has been shown to be substantially higher than for AD patients with no co-morbidities, with 75% of that higher cost attributed to higher inpatient and skilled nursing facility costs (Hill et al., 2002a). However, improving the cognitive and behavioural symptoms of AD can lead to more effective and cost-effective management of co-morbid conditions in AD patients, at least in part because of improved adherence to therapy for the co-morbid condition and consequently a reduced need for additional intervention (Hill 2002b). Thus, improving the symptoms of AD and delaying its progression from the early to the more advanced stages of the disease may not only reduce the burden and costs associated with AD itself (see below) but also the differential burden that results from the management of co-morbid conditions.

1.7. Caregiver Burden

Symptomatic treatment of mild AD delays the onset of the behavioural disturbances of AD that are most troublesome to caregivers, resulting in good patient and caregiver quality of life for longer; reducing caregiver burden; and thus deferring costly institutionalisation.

Informal care from family caregivers provides the foundation of care for most patients with AD worldwide. It has been estimated that 63.5% of people with late onset dementia in the UK live in private households in the community (Knapp et al., 2007) and that friends and relatives of the 517,000 dementia patients living in the community in the UK provided a total of 1,509 million hours of informal care in 2008 (Luengo-Fernandez et al., 2010). Of this total time spent caring, 34% was provided by economically active and employed family or friends.

Caregivers play a large role in assisting AD patients with ADLs, a role which increases as the disease progresses. However, the Alzheimer's Society (2010) estimates that approximately one-third of all people with dementia in the UK live alone, so maintaining ADLs in these patients is particularly important, where a caregiver is not always at hand. In one study in patients with moderate to severe AD (Feldman et al., 2003), donepezil was associated with a significantly slower decline than placebo in instrumental and basic ADLs. As a result, the caregivers of the donepezil-treated patients reported spending, on average, 52.4 minutes less per day assisting with ADLs than the caregivers of the placebo-treated patients. For AD patients who live alone, symptomatic treatment that improves ADLs, and thereby patients autonomy, is particularly crucial.

Several studies have highlighted the negative effects that caring has on caregivers including poor carer health and high levels of mental stress. A high prevalence of depression among the carers of older people has been reported (Livingston et al., 1996). Caregivers of AD patients have been reported to make 46% more visits to physicians and to use 71% more prescription drugs than matched controls (Haley et al., 1987).

Caregiver burden is more strongly associated with the behavioural disturbances of AD than with the cognitive symptoms (Kaufer et al., 1998). There is a significant body of evidence that AChEIs are associated not only with improvements in cognition but also the behavioural symptoms of AD. Donepezil has shown efficacy in improving the neuropsychiatric symptoms of AD (Campbell et al., 2008; Holmes et al., 2004) including delusions (Fischer et al., 2006), apathy (Feldman et al., 2001; Boyle and Malloy, 2004), agitation/aggression (Tariot et al., 2001) and depression and anxiety (Feldman et al., 2001; Gauthier et al., 2002), and in so doing, has concomitantly reduced

caregiver burden (as measured by levels of caregiver stress; Holmes et al., 2004; Feldman et al., 2003).

Further, caregiver burden (produced largely by the behavioural symptomatology of AD) is an important determinant of patient institutionalisation (Haupt and Kurtz, 1993; Hope et al., 1998; Smith et al., 2001; Torti et al., 2004) and interventions that reduce caregiver burden have been shown to delay nursing home placement of patients with AD (Mittelman et al., 2006). Indeed, a strong association between duration of sustained use of donepezil and delay in time to nursing home placement has been seen; specifically patients in the early or intermediate stages of AD who received ≥5 mg/day donepezil for at least 9 to 12 months had a delay to temporary and permanent nursing home placement of almost two years compared with patients who did not receive effective therapy (≥5 mg/day for the requisite study period; Geldmacher et al., 2003).

Maintaining the patient's independence and delaying institutionalisation are core precepts of AD management for people with dementia and their carers (Department of Health, 2009). AD caregivers consider delaying nursing home placement to be extremely or very important (Karlawish et al., 2000). Moreover, patients cared for and managed in the community have been found to be less dependent, show less depressive symptomatology, are more mobile, engage in verbal communication more frequently and have fewer language difficulties than those in hospital care, even when there is no difference in terms of dementia severity (Ritchie 1992). Thus, maintaining AD patients in the community is itself associated with a better health outcome.

Symptomatic treatment of AD improves the behavioural disturbances of AD that most contribute to caregiver burden. The consequences of this are far-reaching in terms of reduced caregiver distress, deferred institutionalisation and enhanced patient and caregiver quality of life. Moreover, the earlier that treatment can be commenced in the course of the disease, and the longer difficult behavioural symptoms can be postponed, the better the outcome for patient and carer. In a corollary, it seems likely that adherence to any treatment becomes less likely as the disease progresses and cognition and behaviour deteriorate, making early initiation of treatment all the more compelling.

1.8. The Socio-Economic Burden of Alzheimer's Disease

Dementia cost the UK economy £23 billion in 2008 rising to £34.8 billion by 2026. Of the total, long-term care costs constituted 40% and informal care (opportunity costs of unpaid care), 55%. However, health care costs (primary care; inpatient and outpatient costs; A&E; medications) accounted for only 5% of the total.

AD represents a significant economic burden across industrialised countries with a substantial impact on healthcare systems and the public purse as well as on patients and their families. Dementia is estimated to cost the UK economy £23 billion per year (Luengo-Fernandez et al., 2010), which is more than cancer, stroke and coronary heart disease combined. Moreover, the National Audit office has predicted that the cost of dementia will rise to £34.8 billion by 2026 (National Audit Office, 2010) as a result of the fact that the number of people with dementia is expected to double within 30 years.

The total cost of AD is estimated to consist of (Luengo-Fernandez et al., 2009):

- Social care costs (long-term nursing and residential care; 40% of total cost);
- Health care costs (primary care, A & E visits, outpatient and inpatient care, medication and private care; 5% of total cost);
- Indirect costs (or informal costs including hours of unpaid care provided by carers, working years lost (mortality) and incapacity days (morbidity); 55 % of total cost).

Of the total, the care of an estimated 305,000 patients in long-term institutions in the UK is estimated to cost in excess of £9 billion per year, approximately £30,000 per patient per year; health care costs are £1.2 billion of which hospital inpatient stays account for 44%. Unpaid carers provide a total of 1.5 billion hours of unpaid care. With an estimated monetary value of £12.4 billion, unpaid care constitutes the single largest component of the total cost of AD (Luengo-Fernandez et al., 2010). The deteriorating health of the caregiver and their growing use of healthcare resources add to the direct costs of AD that are incurred by the NHS.

It is notable that drug costs – estimated to be £228 million in 2008 – are only a small proportion of the total economic burden of AD to the NHS and society (Luengo-Fernandez et al., 2010). There is evidence that, even accounting for its inherent cost, drug treatment reduces overall AD care costs (Wimo et al., 2003; Feldman et al., 2004). Donepezil treatment in patients with moderate and severe AD has been linked to reduced indirect costs as caregivers are required to spend less time assisting patients with ADLs (Feldman et al., 2003; 2004). In addition, as discussed in section 1.5 above, maintaining treatment with an effective dose of donepezil keeps patients in the community longer, preventing expensive institutionalisation and reducing the total costs of AD. Importantly, although AChEIs have been associated with a significant reduction in risk of entry to nursing homes, no association has been found between AChEI use and time to death (Lopez et al., 2002). This has important public health and cost implications. Cost savings made as a result of delayed institutionalisation are therefore not negated by the patient requiring care for a longer period of time.

AD is most costly in the later stages, when patients' symptoms are most severe. Delaying progression to the more advanced and more costly stages of the disease through effective symptomatic treatment in the early stages is a cost-effective approach to the management of AD.

1.9. Managing Alzheimer's Disease in Clinical Practice in the UK

In February 2009, the government published its first ever national dementia strategy (*Living Well with Dementia: A National Dementia Strategy*) whose aim is to ensure that significant improvements are made to dementia services across three key areas: improved awareness, earlier diagnosis and intervention, and a higher quality of care.

NICE currently recommends the use of three AChEIs, donepezil hydrochloride, rivastigmine and galantamine as one component of the management of people with moderate AD, where moderate is defined by NICE as an MMSE score of 10–20 points.

In the UK more money is spent on anti-psychotic drugs for AD patients (£128 million) than on the 4 anti-dementia drugs (£100 million) amid concerns that anti-psychotics are being prescribed inappropriately in many of these patients.

1.9.1 Progress in Management of Patients with AD

A number of initiatives addressing the management of AD have been launched in the years since the 2004 NICE submission. These include a joint clinical guideline on the management of dementia published by NICE and the Social Care Institute for Excellence (SCIE) (NICE, 2007) and, in June 2008, a £255 million Carers' Strategy, including the piloting of annual health checks for carers and training for GPs to recognise and support carers. Undoubtedly, the publicity surrounding the NICE 2006 guidance on the use of the three AChEIs as a part of the management of people with moderate AD (NICE 2006) has been an important contributor to the growth in awareness of AD and services available for people in the UK with dementia over the last few years. For example, the National Audit office (2010) reports that in 2009 87% of GPs said they could access a memory clinic, compared with 69% in 2007. Moreover, as reported, appropriate prescribing of AChEIs increased by 28% over the 3 years since the 2006 guidance was issued.

In February 2009, the government published its first ever national dementia strategy (*Living Well with Dementia: A National Dementia Strategy*). It identifies 17 key objectives which, when implemented, largely at a local level, should result in significant improvements in the quality of services provided to people with dementia and should promote a greater understanding of the

causes and consequences of dementia. Among these key objectives are: improving public and professional awareness; good quality early diagnosis and intervention for all; easy access to care; improved quality of care in general hospitals; and implementing the carers' strategy. An accompanying implementation plan for the strategy involves support at a national, regional and local level provided by the Department of Health. In addition, NICE is currently in the process of developing quality standards in dementia (NICE, 2010).

The Quality and Outcomes Framework (QOF) is a component of the new General Medical Services contract for general practices, introduced on 1 April 2004. The QOF measures practice achievement against a range of evidence-based clinical indicators and against a range of indicators covering practice organisation and management. On the basis of the results practices are rewarded financially for the provision of quality care, and further improvements in the delivery of clinical care funded.

1.9.2 Pharmacological Treatments in AD Patients

In 2006 NICE (NICE TA111 and Clinical Guideline 42) recommended the AChEIs, donepezil, galantamine and rivastigmine, as options in the management of people with AD of moderate severity (where moderate severity was defined by NICE as a MMSE score of 10–20 points), under the following conditions:

- Only specialists in the care of dementia should initiate treatment.
- Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment.
- Carers' views on the patient's condition at follow-up should be sought.
- The drug should only be continued while the patient's MMSE score remains at or above 10 points and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect.

NICE further stipulated that people with mild AD already receiving donepezil, galantamine or rivastigmine, and people with moderately severe to severe AD already receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist consider it appropriate to stop. Subsequent amendments addressed the use of the MMSE in patients with linguistic, learning or communication difficulties (September 2007) and reviewed the economic model used to evaluate the cost effectiveness of donepezil (August 2009). Neither amendment altered the recommendation that donepezil should be prescribed to patients in only the moderate stages of the disease as defined by NICE as an MMSE score of 10–20 points.

Although the number of prescriptions for AChEIs did increase over the 3 years to 31 March 2009 (National Audit Office, 2010), the proportion of patients receiving an AChEI in the UK may be less than half that in countries such as Spain, Ireland, France and Sweden (Waldemar et al., 2007). This is the consequence of sometimes stark differences between the approaches of different European countries towards the management and treatment of AD, in particular varying recommendations as to reimbursement for anti-dementia drugs. For example, France requires the initial AChEI treatment decision to be made by a specialist, but does not dictate how the decision to continue treatment should take place. In both Ireland and Germany, AChEIs are reimbursed with no restrictions as to who makes initial or continuing treatment decisions, and no imposition of MMSE limits on treatment.

Moreover, it is of note that more money is spent in the UK on anti-psychotic drugs for AD patients than on the 4 anti-dementia drugs (£100 million was on the 4 anti-dementia drugs (donepezil, rivastigmine, galantamine and memantine) and £128 million on anti-psychotic drugs in 2008; Leungo-Fernandez et al., 2010). While anti-psychotic prescription to AD patients is necessary in certain circumstances for controlling some of the symptoms associated with AD, such as sleeplessness and agitation, an independent review has reported that up to 150,000 people with dementia are prescribed anti-psychotic drugs contrary to clinical guidelines (Banerjee, 2009). NICE stipulates that people with AD, vascular dementia or mixed dementias with mild-to-moderate non-cognitive symptoms should not be prescribed anti-psychotic drugs because of the possible increased risk of cerebrovascular adverse events (AEs) and death (NICE, 2007). In older patients, in general, there is potential for increased sensitivity to drug-related AEs when medications are co-administered with anti-psychotics. This enhanced sensitivity is caused by reduced drug metabolism, the presence of co-morbidities, and additive pharmacologic effects of concomitantly administered drugs. It has been estimated that prescribing of anti-psychotic medications to dementia patients may contribute to 1,800 additional deaths each year (Banerjee, 2009).

As discussed in section 1.5 above, AChEIs are associated with improvements in the neuropsychiatric symptoms of AD. Therefore, it is reasonable to expect that these behavioural improvements produced by AChEI use would obviate the need for anti-psychotic medication. Indeed, there is evidence that AD patients treated with the AChEI, rivastigmine, have a reduced risk of being treated with anti-psychotic drugs compared with patients who receive no AChEI treatment (Narayanan et al., 2006; Suh et al., 2004). Unfortunately, the design of these studies by Narayan and Suh precluded any means of capturing information on the clinical severity of dementia and outcomes, which could be confounding factors. However, the fact that only patients who were newly diagnosed with AD and who had not used anti-psychotic drugs during the 18 months prior to their index date were included in the study by Suh and coworkers (2004)

suggests that these patients were towards the mild end of the AD spectrum. In the study by Narayan and coworkers (2006), only newly admitted nursing home residents who were naive to antipsychotic treatment during the month before rivastigmine initiation or first AD diagnosis were included in the analysis. This implies that AChEI use may reduce anti-psychotic use even in AD patients with mild disease.

In another study, 51% of patients had discontinued or decreased the use of their psychoactive medication at follow-up, following initiation of treatment with rivastigmine (Verny et al., 2004). In an observational study of patients whose mean baseline MMSE score was almost 19 (where an MMSE score greater than 20 is considered mild by NICE), those never exposed to AChEIs used more anti-psychotic drugs at baseline and at follow up compared with those who used AChEIs (Lopez et al., 2002), suggesting that even at the mild end of the AD spectrum, AChEI therapy is associated with less anti-psychotic use. Donepezil use has also been associated with a reduced need for psychotropic medications (Small et al., 1998).

Thus, initiation or maintenance of donepezil therapy results in improved behavioural symptoms among AD patients which (1) reduces caregiver burden, thereby delaying institutionalisation (Geldmacher et al., 2003; Mittelman et al., 2006); and (2) reduces the use of anti-psychotic medication (Small et al., 1998), thereby decreasing morbidity and mortality. Donepezil is licensed for the symptomatic treatment of mild to moderately severe AD and its license states that maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists (see SmPC for donepezil in Appendices A and B). It should be noted that decline that is less than expected or less than would be seen if the patient remained untreated is considered a treatment benefit. NICE currently recommends that treatment with an AChEI should normally only be continued while the patient's MMSE score remains above 10 points and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. As previously discussed, decision making as to appropriate treatment strategies on the basis of a single assessment tool (MMSE) is not in the individual patient's best interest. Assessing the benefit of donepezil therapy in the later stages of AD is a difficult clinical decision for a specialist and it should not be stopped on the basis of a crude MMSE score alone. Indeed, to do so may be harmful to the patient, resulting in behavioural deterioration and possibly increasing the risk of anti-psychotic drug use, contrary to the aims of the *National Dementia Strategy*.

1.9.3 Continuing Barriers to Effective Management of AD

In spite of promising initiatives and evidence of a growing awareness of the challenges of AD, there are significant shortcomings in the management of AD patients in the UK. Although one key goal of the *National Dementia Strategy* is early diagnosis, there remains a significant gap in the

UK between the expected number of people with dementia and the number of people diagnosed: overall, only one third of people with dementia receive a formal diagnosis or have contact with specialist services at any time during their illness (Department of Health, 2009).

In the UK the lead specialty that has evolved to diagnose and treat people with dementia is old age psychiatry although a geriatrician, neurologist, GP or psychiatrist (including those specialising in learning disabilities) may also play a role. There remains widespread reticence among GPs to make a diagnosis of dementia in primary care (Vernooj-Drassen et al 2005) and there is marked variation in their skills in diagnosing and managing dementia (O'Connor et al 1988, Philp and Young 1988). The National Audit Office (2010) reports that in 2009 28% of GPs were not very confident about making a diagnosis of dementia, and 42% reported not feeling confident about advising patients on dementia management. Diagnosis is the gateway to care without which, the person with dementia and their family carers are denied the opportunity of making informed choices concerning the management and treatment of the illness while they have the capacity to do so. Moreover, they are unable to make informed plans for their future and are effectively denied access to any help, support and treatments (social and psychological, as well as pharmacological) available.

Most patients in the UK are primarily managed in secondary care where there is a serious shortage of specialist staff able to diagnose, treat and manage AD. In 2007, the lack of joined-up health and social care planning and delivery was identified as a barrier to improvements in dementia care (Knapp et al., 2007). In the current scenario, people with dementia are still being unnecessarily admitted to hospital, have longer lengths of stay and enter residential care prematurely.

In spite of the NICE 2006 guidance, the National Audit Office (2010) reports that regional variations in prescribing of AChEIs persist. Between October 2005 and September 2006 there was a 30-fold difference in the number of prescriptions for the 4 anti-dementia medications (the AChEIs, donepezil, rivastigmine, and galantamine; and memantine) across England and Wales, between the Primary Care Trust (PCT) with the highest number and the one with the lowest number (Knapp et al., 2007). This is indicative of continued variation in the way in which AD is assessed and treated across the UK.

1.10 Goals of the Current Submission

While there is no cure for AD, its onset and the advent of the most distressing and burdensome symptoms in the more severe stages of the disease may be delayed through a combination of improvements in public health and pharmacological treatments. Rapid intervention to treat and manage dementia ensures the best outcome for patients and delays in assessment and

treatment, by even a few months, have a negative impact on patient outcomes. Available pharmacological treatments have demonstrated efficacy in delaying symptomatic progression to the more severe stages of the disease. The goal of pharmacological treatment is to provide symptomatic relief for as long as possible and to improve, maintain or at least slow down the rate of decline and deterioration in cognition, behaviour and functional ability. Patients are regarded as responding to treatment if one of these outcomes is attained across any of these domains, although the periodic re-assessment of response that is stipulated in NICE guidance, TA111 (see section 1.7.1. above) is based principally upon MMSE score.

Although NICE guidance, TA111, has served to increase awareness of AD and has resulted in increased prescription of AChEIs, Pfizer and Eisai believe that the guidance can better meet the needs of AD patients and align with the goals of the National Dementia Strategy through the following:

- AChEIs should be available to AD patients from the earliest stages of the disease. The consequences of enabling access to treatment for patients with mild AD are:
- the AD patient experiences the impact of AChEIs (maintained cognitive function; a reduction in behavioural symptoms; and prolonged autonomy) on their quality of life for longer;
- patients' function is maintained for longer, reducing the caregiver time spent assisting with ADLs, and thereby reducing the economic burden on the caregiver and maintaining their quality of life;
- the onset of behavioural symptoms are delayed thereby reducing caregiver burden, in turn delaying expensive institutionalisation; and also reducing the use of anti-psychotic medication;
- reduced caregiver burden may reduce health care needs and so reduce direct costs to the NHS;
- better drug adherence by the AD patient means better and more cost-effective management of co-morbid conditions.

We consider that the absence of any recommendation for treatment of AD in the mild stages reduces the impetus for early diagnosis and management thereby undermining the aims of the *National Dementia Strategy*. If patients with AD in the mild stages could be prescribed AChEIs, then one could expect a greater willingness/interest in early diagnosis, in accordance with the *National Dementia Strategy*.

Extending donepezil treatment to patients in the mild stages of the disease will reduce the overall costs of AD as costly institutionalisation is deferred and the indirect costs associated with

caregiver time are reduced. Moreover, we expect that actual drug costs will fall as donepezil and other AChEIs go off patent in early 2012.

The assessment and clinical management of AD patients should not be conducted according to MMSE score alone. Decisions concerning patient treatment – whether to initiate or continue therapy– should be based on clinical assessment of individual need. Patients in whom AChEI treatment was initiated in the mild and moderate stages of the disease should not have treatment discontinued at an arbitrary MMSE of 10. To do so is not in agreement with the AChEI licences and does not take into account that AD is not characterised by cognition alone and that physical functional and behavioural symptoms are also important. Assessing the benefit of continuing treatment with an AChEI is a difficult clinical question that should not be undertaken based on crude MMSE guidance but which instead considers the potential for harm to the patient.

NICE guidance is a critical part of dementia care in England and Wales. There has been no recent advice on drug therapy and the next NICE guidance on “Drugs for the Treatment of AD” will be referred to by clinicians at all levels for several years to come. This guidance should facilitate the realisation of the goals of the *National Dementia Strategy*.

SECTION 2 – CLINICAL EFFECTIVENESS OF DONEPEZIL

2.1 Executive Summary

- Donepezil has been investigated in a large number of clinical trials and observational studies. Presented here is the trial evidence published since 2004 and a summary of trials from the previous two submissions. In all, 12 placebo-controlled RCTs, three head-to-head RCTs and six meta-analyses of trial data are presented. In addition, non-RCT evidence published since 2004 is presented consisting of two prospective longitudinal studies, and 3 observational studies
- A pooled meta-analysis of patient level data from 11 trials confirmed significant benefits in cognition for patients with mild AD treated with donepezil compared to placebo.
- Another pooled meta-analysis of ten trials showed that donepezil led to a significant improvement in global function compared with placebo in both mild and moderate AD. This analysis also showed a greater benefit from donepezil treatment may be observed in mild rather than moderate disease and that earlier treatment may be associated with greater preservation of function.
- All 12 placebo-controlled RCTs report on the domain of cognition and all found a significant advantage for donepezil versus placebo.
- Of seven RCTs reporting on the function domain, four reported a statistically significant difference favouring donepezil versus placebo on at least one scale, while the other three reported non-significant trends in favour of donepezil. In addition, a recently published meta-analysis of seven donepezil RCTs found a statistically significant advantage favouring donepezil versus placebo on the function domain.
- Of seven RCTs investigating the effects of donepezil on the behavioural symptoms of AD, three found a significant difference between donepezil and placebo on the Neuropsychiatric Inventory (NPI) score. In addition, a recently published meta-analysis of donepezil RCTs found a statistically significant difference in favour of donepezil compared with placebo on the NPI total score.
- Two RCTs and one observational study demonstrate that improvements in neuropsychiatric symptoms that are produced by donepezil are accompanied by a reduction in levels of caregiver stress and burden. In a sub-analysis of a one-year RCT, time spent caring for patients with AD was approximately one hour per day less for the caregivers of patients who received donepezil compared with those who received placebo.
- Two prospective longitudinal studies in patients with mild to moderate AD show that the beneficial effects of donepezil on cognition and function are maintained for at least 3 years. Two RCTs and one prospective longitudinal study also demonstrate that the benefits of

donepezil treatment are lost rapidly upon cessation of treatment and (particularly neuropsychiatric) symptoms re-emerge.

- One RCT found that an initial decline or stabilisation in MMSE score is not necessarily indicative of a lack of treatment effect. Discontinuation of treatment should therefore be based on specialist assessment of the individual patient and must not be based a single assessment parameter such as crude MMSE score.
- One double-blind head-to-head RCT and a Cochrane review indicated that the magnitude of clinical effect is similar across the AChEI class, but a more favourable tolerability profile for donepezil compared with the other AChEIs has been observed.
- A double-blind, placebo-controlled RCT demonstrates that continued donepezil therapy with the addition of memantine is a beneficial treatment strategy.
- Given the evidence that patients with mild AD experience cognitive and functional benefit from donepezil, treatment should be initiated as early in the disease as possible to delay symptomatic progression and realise optimal clinical benefit.

2.2 Methods for the Identification of Relevant Clinical Evidence

This chapter presents clinical evidence for the use of donepezil in the symptomatic treatment of mild to moderately severe AD that has become available since the 2004 NICE submission and contextualises this in relation to the pre-2004 evidence base for donepezil. The new evidence has been identified from a systematic review of the literature. The objectives, methods and results of this review are briefly discussed below in *Sections 2.2.1 to 2.2.4*. Thereafter the new evidence identified in this review is presented in Sections 2.3 and 2.4.

2.2.1 Literature Search Objectives

The present submission has taken a targeted approach to the identification of clinically relevant evidence published since 2004.

Initially a broad literature search was conducted to identify:

- Relevant randomised controlled trials (RCTs) of mild to moderate Alzheimer's Disease (AD) patients that included a donepezil treatment arm.
- Prospective longitudinal studies of mild to moderate AD patients treated with donepezil for more than two years in order to capture important longer-term efficacy and safety data. Two years was selected as the inclusion criterion, to capture additional data to supplement the RCTs evidence base that was available up to two years for donepezil.
- Observational studies of donepezil and other AChEIs in patients with any stage of AD was that addressed the following clinically important questions:
    - Is there any benefit of continued use of AChEIs irrespective of severity in terms of prevention of increased use of anti-psychotics?
    - Is there any evidence of harm resulting from discontinuation of AChEIs at any stage of illness?
    - Is there any observational evidence on caregiver burden for AChEIs as a class?
- Meta-analyses of RCTs investigating AChEIs in AD published between 2008 and 2010.

The electronic databases used and key search terms for each literature search are summarised briefly in *Section 2.2.2* below.

2.2.2 Literature Searches and Data Sources

The literature search included both electronic and manual components. Electronic searches were performed in MEDLINE (via PubMed) and EMBASE for periods between January 2004 and January 2010 using indexed key words using the appropriate syntax for each database. The searches were limited to the English language.

Additionally, the Cochrane Library was searched for recent systematic reviews that included a focus on AChEIs on AD to provide a source of further references. A manual check of the reference lists of all accepted papers and of recent reviews and meta-analyses was performed to supplement the electronic searches. The Cochrane Dementia and Cognitive Improvement Group's (CDCIG) Specialised Register was also searched for studies that may not be indexed in the above mentioned sources.

The searches were conducted on January 21, 2010. The full literature search strategies are available in Appendix C.

2.2.3 Study Selection and Data Extraction

The precise methods of study selection described in the correlated protocol (Appendix C) are briefly summarised below.

Potentially relevant studies included those reporting clinical effectiveness analyses of donepezil in patients with AD with or without comparison to another AChEI. Study selection was accomplished through two levels of study screening. Titles and abstracts were screened for obvious exclusion criteria (e.g. no AD patients) and potential relevance. Thereafter, the full articles of accepted titles and abstracts that passed abstract screening were retrieved for further review. All studies accepted or rejected at full-article screening required the consensus of two independent investigators. All the studies that were accepted at full-article screening were eligible for inclusion in the clinical effectiveness chapter in the current submission.

During the initial filter process, a large number of studies were included from the systematic literature searches in order to ensure that no relevant studies were missed. Thereafter, more specific exclusion and inclusion criteria were applied to select the best clinical evidence with appropriate focus.

The following inclusion and exclusion criteria were applied:

Inclusion criteria for meta-analyses:

- Pooled analyses of RCTs focusing on AChEIs in AD patients

- Published between 2008 and 2010

Inclusion criteria for RCT's/longitudinal prospective studies:

- In accordance with the license for donepezil, studies of patients undergoing treatment with donepezil (in at least one arm) where initiation occurred during the mild and moderate stages of AD. This includes combination studies in which memantine was added on top of stable donepezil treatment
- RCTs (double-blind) or prospective longitudinal studies (cohort or open-label extensions of at least 104 weeks duration) reporting outcomes regarding:
    - Clinical response (CR)
    - Time until institutionalisation
    - Time until change in severity of dementia stage
    - Time until full-time care is necessary
    - Time until death
    - Adverse events
        - Total discontinuation, withdrawal due to adverse event
        - Number of patients with severe adverse events
    - Mortality
    - Cognitive function measures
    - Global function measures
    - Activities of daily living, quality of life, and behavioural disturbance measures
    - Caregiver burden measures

Inclusion criteria for observational studies:

Prospective and retrospective observational studies of donepezil alone or compared to any other AChEI in any stage of AD reporting outcomes addressing at least one of the three clinically important questions outlined above (*Section 2.2.1*).

Exclusion Criteria for all studies

- Animal or *in vitro* studies
- Letters, comments, case-reports, or editorials
- Reviews published before 2008
- Studies published before 2004
- Languages other than English

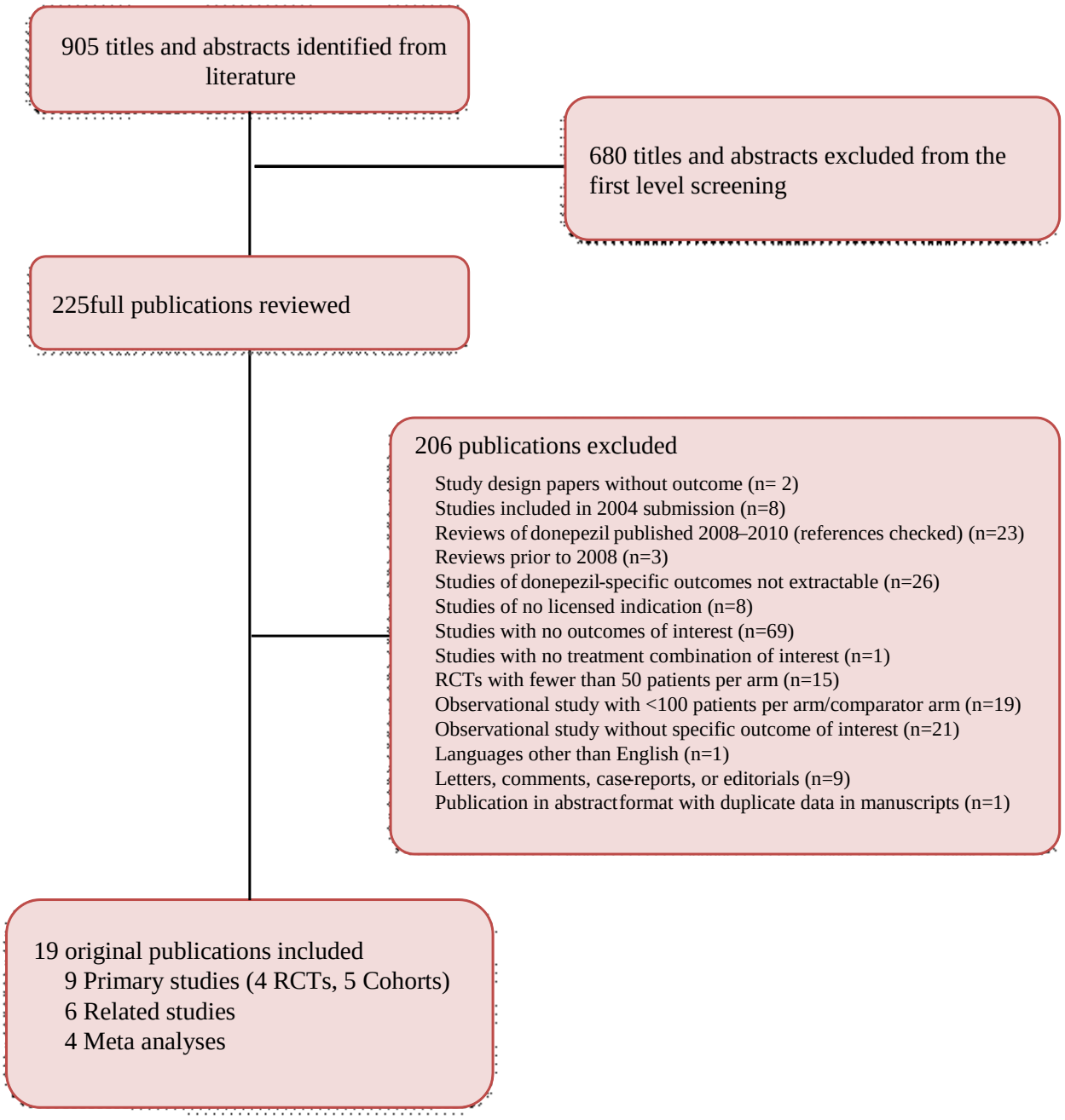
- Pharmacokinetics or pharmacodynamics studies
- RCT with fewer than 50 patients per treatment group or with treatment duration less than 12 weeks
- Observational study with fewer than 100 patients in the donepezil group or fewer than 100 patients in all comparator groups
- Study already included in the 2004 submission
- Study with comparators other than AChEI, e.g. Gingko biloba
- Study with non-licensed indications (includes studies where donepezil was initiated in the severe stages of the disease)
- Study with non-licensed dosages
- Study reporting the effects of other interventions (such as counseling), with both treatment arms on donepezil baseline therapy ("no outcomes of interest")

2.2.4 Review Results

The broad literature search yielded 905 citations, excluding duplicate citations from the various sources. In addition, a total of 133 citations were obtained from the CDGIC database search. However, after checking these against the citations from the literature database searches, no additional studies were identified. The number of citations yielded from each database is presented in Appendix D.

Of the 905 citations, 680 abstracts were rejected during Level I screening while 225 were accepted and full papers retrieved. Of the 225, 19 were accepted on application of the study inclusion and exclusion criteria outlined in section 2.2.3 above. After determining which studies were related publications, the final database of accepted studies consisted of nine primary research studies and six related publications. In addition, four meta-analyses providing relevant pooled outcomes data were included. The complete flow of study attrition is shown in Figure 1 below. Citations of all accepted studies and corresponding links are provided in the attached Accepted Studies Log (See Appendix D). Of the 225, 206 studies were rejected and the citations for these studies rejected at Level II are listed in the attached Rejected Studies Log, along with the reason for rejection (See Appendix D). The attrition flow diagram including the reasons for study rejection is also shown in Figure 1 below.

Figure 1 Flow chart for identification of studies in the systematic review



The clinical evidence identified in the clinical effectiveness search will be discussed in Section 2.3 below. Thereafter, the evidence identified in the targeted observational studies search will be discussed in Section 2.4 below.

2.3 Output from Clinical Effectiveness Search

2.3.1 An Overview

Of the nine primary research studies identified by the clinical effectiveness search strategy, three were RCTs (Courtney 2004, Bullock 2005, Tariot 2004); one (Wimo, 2004) was a subanalysis of an RCT presented in the 2001 submission (the Nordic study; Winblad et al., 2001); two were prospective longitudinal studies (Burns 2007, Wallin 2007); and three were observational studies addressing specific research questions (Tanaka, 2008; Riepe, 2007; Gasper, 2005). The three RCTs were: one placebo-controlled RCT of donepezil (Courtney, 2004); one comparing donepezil and rivastigmine (Bullock, 2005) which has been published along with two subanalyses (Bullock, 2006; Touchon, 2006); and one RCT of memantine on top of stable donepezil therapy (Tariot et al., 2004, with three subanalyses (Cummings 2006, Feldman 2006, Schmitt 2006)). The subanalysis (Wimo et al., 2004) was based on a 52-week placebo-controlled trial of donepezil and focused on caregiver time burden over this period. These are summarised (methods, participants and outcomes) in Table 1 below. No new pooled analyses were conducted due to the paucity of new RCT evidence. Instead, our literature search has identified four meta-analyses (two systematic reviews (Hansen, 2008; Campbell, 2008); two pooled analyses (Burns, 2008; Wilkinson, 2009)) published between 2008 and 2010. Their characteristics and findings are summarised in *Section 2.3.2* below in relation to outcomes relevant to this submission. Two additional meta-analyses, evaluating the effects of donepezil in mild AD patients (Murthy, 2008; Prodafikas, 2009), were provided by the manufacturer. As these are only available as conference abstracts, they were not identified in the literature searches, but since few donepezil trials have focused exclusively on patients with mild AD, these are included in our evidence base for donepezil and are also included in *Section 2.3.2*.

The new studies identified in this submission are in addition to the existing large evidence base identified in the two previous submissions which has established donepezil as the standard of care for the symptomatic treatment of mild to moderate AD.

In 2001 the evidence presented (17 studies in total) consisted of an independent systematic review of 10 phase II and III double-blind, placebo-controlled RCTs of donepezil (5 and 10 mg/day) completed and reported as of December 1999. In addition, the results from four of the

RCTs used in the systematic review were presented individually (Studies 201: Rogers 1996, 301: Rogers 1998a, 302: Rogers 1998b, and 304: Burns 1999), along with the results from four randomised, placebo-controlled post-registration studies (the Nordic Study: Winblad 2001, Moderately Severe Alzheimer's Disease study (MSAD): Feldman 2001 and Feldman 2003, the Nursing Home Study: Tariot 2001, and the Functional Survival Study, Mohs 2001); and two open-label extension studies (Study 202: Rogers 1998c and Rogers 1998d, an extension of Study 201; and Study 303: Doody 2001, an extension of Studies 301 and 302). Only one non-randomised study was included in the 2001 dossier – the Experience Study (McRae 1998), an open-label, multicentre clinical trial evaluating the safety and efficacy of donepezil in a more routine clinical practice setting.

In the 2004 NICE submission, seven placebo controlled RCTs (Feldman 2001, Feldman 2003, Selzter 2004, Johannsen 2006, Holmes 2004, Prasher 2002 , Black 2003, Wilkinson 2003,); two direct comparator trials (Jones 2004, Wilkinson 2002); and eight non-randomised and observational studies (Geldmacher 2003, Lopez 2002, Winblad 2006, Boada-Rovira 2004, Jones and Wilkinson (unpublished), Klinger 2005, Riepe 2003, Kohler 2003, Frolich 2002) completed since the 2001 submission were described. The latter evaluated issues that included delays to nursing home placement; impact of persistent and early treatment; response to switching and withdrawal of treatment; and effectiveness in dementia with concomitant cerebrovascular disease.

It is notable that the primary outcomes of the two new placebo controlled RCTs (delay to institutionalisation and caregiver time) differ from those of the Phase II and III RCTs reported previously in which the primary outcome measures were changes in measures of cognition and function. Changes in measures of cognition and function are measured in one of these RCTs (Courtney, 2004) as secondary outcomes.

It is noteworthy that the newly identified placebo-controlled RCTs of donepezil are of at least two years duration, consistent with the realisation that in chronic diseases long-term studies are required to perceive meaningful clinical trends. Indeed, two pivotal placebo-controlled RCTs reported in the 2004 submission (Winblad et al., 2001; Mohs et al., 2001) were also of one-year duration and demonstrated statistically significant benefits for donepezil relative to placebo in measures of cognition and function. Since then, placebo-controlled designs that exceed six months duration in international AD treatment studies are no longer considered ethical; hence the small number reported here. Studies of short duration are less informative about whether donepezil can delay the progression of the disease or about the consequences of longer-term use. The alternative is to conduct long-term open-label extensions of closed studies or observational studies in the routine clinical setting. While the placebo-controlled RCT has been

regarded as the gold standard study design, observational studies are relevant to clinical practice due to their use of wide inclusion criteria. Moreover, the acceptance of coexisting illnesses and concurrent medication produces a more representative cohort of patients than are usually included in conventional clinical trials. Thus, the results of such trials may be readily applicable to ordinary patients.

Hence in this submission, some of the new evidence derives from large, prospective, longitudinal studies of donepezil in the clinical setting. This includes one open-label extension study (Burns, 2007) evaluating the efficacy and safety of donepezil over a three-year period and one observational study of donepezil use of more than two years duration (Wallin et al., 2007; subanalysis in Persson et al., 2009).

First, we present the evidence from the six meta-analyses (*Section 2.3.2*). Then, we present the methods and findings of the new RCTs (*Section 2.3.3*) and prospective longitudinal studies (*Section 2.3.4*) followed by evidence from four observational studies (Section 2.4).

2.3.2 Evidence from Meta-Analyses

Four meta-analyses of donepezil RCTs (Burns et al., 2008; Campbell et al., 2008; Hansen et al., 2008; Wilkinson et al., 2009), the results of which were published between 2008 and 2010 were identified as part of the literature search and are described here. In addition, two recent meta-analyses of individual patient data from the donepezil clinical development program in the form of conference abstracts provided by the manufacturer are included (Murthy et al., 2008; Prodafikas et al., 2009). Many of the same RCTs are included in these meta-analyses, though not always in the same combination. In addition, they evaluate different outcomes. The Murthy meta-analysis evaluated the effect of donepezil on cognition using MMSE and ADAS-cog in patients with mild AD only, while the Prodafikas meta-analysis (Prodafikas 2009) evaluated the effect of donepezil on global function in patients with mild AD or moderate AD. Wilkinson (2009) evaluated clinical worsening while Burns (2008) performed a responder analysis. Campbell (2008) evaluated the effect of the three AChEIs together and separately on NPI score and Hansen (2008) performed a meta-analysis of placebo-controlled RCTs of each of the three AChEIs in the domains of cognition, function, behaviour and global clinical change.

2.3.2.1 Donepezil in Mild AD: Effects on Cognition

The donepezil clinical trial database was searched for studies that included patients with mild AD and, once identified, patients with baseline MMSE scores of between 21 and 26 were included for this meta-analysis (Murthy et al., 2008). This yielded 11 eligible placebo-controlled RCTs, of which 10 (Homma 2000; Rogers 1996, 1998a, 1998b; Tune 2003; Krishnan 2003; Geldmacher

2000; Burns 1999; Tariot 2001; Mohs 2001; and Winblad 2001) were reported in the 2001 NICE submission and the last (Winblad 2006) was reported in the 2004 submission.

Seven of the 11 studies identified in the Murthy meta-analysis provided data on change from baseline in MMSE score for 723 patients (donepezil: 443; placebo: 280), while eight included ADAS-cog data for 1040 patients (donepezil 690; placebo 350). In the combined patient cohorts mean baseline MMSE scores and mean baseline ADAS-cog scores were very similar for the donepezil and placebo groups. In both observed case and last observation carried forward (LOCF) analyses, and on both the MMSE and ADAS-cog tests, treatment with donepezil in patients with mild AD was associated with statistically significant cognitive gain compared with placebo after both 12 and 24 weeks of treatment. At Week 24 (LOCF) the least squares mean change from baseline in MMSE score was 0.8 (indicating improvement) and -0.51 (indicating decline) for the donepezil and placebo patients respectively ($p < 0.0001$). Corresponding least squares mean changes on ADAS-cog were -1.04 (indicating improvement) and 0.17 (indicating decline) for the donepezil and placebo patients respectively ($p = 0.003$). Thus, following 24 weeks of treatment, cognitive scores of patients with mild AD who had received donepezil were still improved relative to their baseline values, in contrast with those of the patients who had received placebo which had declined over the course of the study.

2.3.2.2 Donepezil in Mild AD: Effects on Global Function

In this meta-analysis (Prodafikas 2009) the donepezil clinical trial database was searched for studies that included patients with mild or moderate AD who had available post-baseline global functional data as measured using the CDR-SB. This yielded 10 placebo-controlled RCTs, of which seven were identical to those in the Murthy meta-analysis. As before, all but one of these RCTs (Seltzer 2004; reported in the 2004 NICE submission), were reported in the 2001 submission (Homma 2000; Rogers 1996, 1998a, 1998b; Geldmacher 2000; Burns 1999; Whitehead 2004; Tariot 2001; Mohs 2001).

These 10 placebo-controlled RCTs provided CDR-SB data from 1195 patients with mild AD (MMSE 21-26; donepezil: 1038; placebo: 707) and 1745 patients with moderate AD (MMSE 10-20; donepezil, 1038; placebo, 707) (Prodafikas 2009). Studies ranged in duration from 12 to 52 weeks. In both the mild and moderate AD cohorts, demographic characteristics and mean baseline MMSE and CDR-SB scores were similar between the donepezil- and placebo-treated patients. In patients with mild AD, the mean change from baseline in CDR-SB scores at study endpoint (LOCF) favored donepezil over placebo (-0.20 vs 0.12, $p = 0.001$). In patients with moderate AD, the mean change from baseline in CDR-SB scores at Week 24 LOCF favored donepezil over placebo (-0.03 vs 0.57, $p < 0.001$). Importantly, at endpoint, treatment with donepezil in the mild cohort was associated with CDR-SB scores that were improved relative to

baseline. In the moderate cohort, CDR-SB scores had worsened by endpoint among patients receiving donepezil, although scores among placebo patients had worsened to a significantly greater degree. This suggests that greater benefit from donepezil treatment may be observed in mild rather than moderate AD and that earlier treatment may be associated with greater preservation of function.

2.3.2.3 An Evaluation of Clinical Worsening

A meta-analysis of three RCTs (Wilkinson 2009) all of which are included in our RCT evidence base (Rogers et al., 1998b; Winblad et al., 2001; Feldman et al., 2001) compared the effect of donepezil and placebo on clinical worsening, defined as any decline in (1) cognition (as measured using MMSE), (2) cognition and global ratings (CIBIC-Plus/GBS scales) or (3) cognition, global ratings and function (the latter being the most stringent definition of worsening). Data were pooled from 906 patients (388 receiving placebo; 518 receiving donepezil) with mild-to-moderate AD. At Week 24, fewer donepezil-treated patients than placebo patients met the criteria for clinical worsening by any definition. With clinical worsening defined as decline in MMSE score, 37.7% and 53.5% of patients who received donepezil and placebo, respectively, were clinically worse at Week 24 (LOCF; $p < 0.0001$). With clinical worsening defined as decline in MMSE score as well as decline in function and global rating, 10.4% and 25.3% of patients who received donepezil and placebo, respectively, were clinically worse at Week 24 (LOCF; $p < 0.0001$). Importantly, among patients meeting the criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients. This suggests that AD patients showing clinical worsening on donepezil may still derive benefits compared with placebo/untreated patients and that many donepezil-treated patients initially characterised as 'non-responders' according to traditional markers of treatment success may still derive benefits (that is, less clinical worsening) over placebo/untreated patients.

In addition, analysis of subgroups of patients with milder (MMSE, 18–26) and more moderate AD (MMSE, 10–17), showed that of patients treated with donepezil, half as many mild patients met the most stringent criterion for clinical worsening (7.2%) as moderate patients (14.4%). Regardless of the definition of clinical worsening employed or the treatment allocation, the percentage of patients showing clinical worsening was greater in the more moderate compared with the milder subgroup.

2.3.2.4 A Responder Analysis

In this meta-analysis (Burns et al., 2008) of five RCTs (Rogers et al., 1998b; Winblad et al., 2001; Burns et al., 1999; Gauthier et al., 2002; Seltzer et al., 2004) in mild to moderate AD patients receiving donepezil 10 mg/day, the authors undertook a responder analysis, where response was defined as improvement or no deterioration in cognitive function together with evidence of

improvement in at least one other measure of global response, function or behaviour. Less stringent definitions of response involved evidence of response on cognitive and functional measures, separately. When ADAS-cog was the primary cognitive assessment, the percentage of responders to donepezil ranged from 26% to 63% and that for placebo from 14% to 47% depending on the definition of responder used (that is improvement in cognition or function only, or cognition plus one other measure). When improvement in cognition plus improvement in function, behaviour or global response was used as the definition of treatment response, then the largest difference between the donepezil and placebo groups in terms of number of responders was seen (34.0% vs. 17.1%). When response was defined as a positive change from baseline on the CIBIC-Plus alone, patients defined as non-responders still demonstrated a mean improvement from baseline in ADAS-cog. This meta-analysis demonstrates higher response rates with donepezil compared with placebo across a number of domains and has important implications for the definition of treatment response**.** It supports the view that disease severity and treatment response cannot and must not be assessed using a single domain or assessment tool.

2.3.2.5 Impact of AChEIs on Behavioural and Psychological Symptoms of AD

In this meta-analysis (Campbell et al., 2008) nine placebo-controlled RCTs of donepezil, rivastigmine and galantamine that evaluated NPI were included. Among patients with mild to severe AD, the AChEIs (donepezil, rivastigmine and galantamine) had a statistically significant effect on the behavioural and psychological symptoms of dementia (BPSD) compared with placebo as measured by the NPI, with a weighted mean difference in NPI scores of −1.38 points (95% CI; −2.30, −0.46). However, in patients with moderate to severe AD there was no statistically significant difference in NPI scores (weighted mean difference of −0.06 (95% CI; −2.12, +0.57) while the largest significant difference between donepezil and placebo-treated patients in NPI score was observed in mild to moderate AD patients (weighted mean difference -1.92 (95% CI; -3.18, -0.66)). Looking at the effect of donepezil separately (six pooled studies) the standard mean difference between donepezil and placebo was statistically significant in favour of donepezil (−1.76 (95% CI: −3.37, −0.15). Among patients with mild to severe AD and in comparison to placebo, AChEIs as a class had a beneficial effect on BPSD.

2.3.2.6 Efficacy and Safety of Donepezil, Galantamine and Rivastigmine for the Treatment of AD

A further meta-analysis identified 22 placebo controlled RCTs of donepezil, rivastigmine and galantamine reporting outcome measures in cognition, function, behaviour, global change and safety (Hansen et al., 2008). A meta-analysis was conducted for each AChEI separately by common outcome measure. Thus, the pooled weighted mean difference between donepezil and placebo (in five studies) was -2.67 (95% CI; -3.28, -2.06) for ADAS-cog; 0.31 (95% CI; 0.21, 0.40) on a measure of function (7 studies); -4.3 (95% CI; -5.95, -2.65) on NPI (four studies); and 1.88

(95% CI; 1.50, 2.34) on CIBIC-Plus (three studies); i.e. statistically significant on all outcomes in favour of donepezil vs placebo. Across the trials, the incidence of AEs was generally lowest for donepezil and highest for rivastigmine.

2.3.3 Evidence from Donepezil RCTs

Table 1 summarises the methods (objectives, assessments, outcome measures) of the RCTs (and their sub-analyses) and the prospective longitudinal studies identified by the current literature search.

Table 1. RCTs and Prospective Longitudinal Studies; Output of Systematic Literature Search and Selection Process

Study Name	Objective(s)	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
RCTs				
AD2000 Study: Long-term donepezil in mild to moderate AD (Courtney 2004)	To determine whether donepezil produces worthwhile improvements in delay to institutionalisation, disability, dependency, behavioural and psychological symptoms, or carers psychological wellbeing in patients with mild to moderate AD.	RCT, DB, placebo-controlled, Multi-centre, 4-phase study. Run-in period: 12-week DB, randomised (5mg donepezil or placebo). Phase 1: 48-week DB, randomised (placebo or donepezil 5 mg or 10 mg) Washout: 6- week no treatment Phase 2: 48-weeks on the Phase 1-assigned treatment (total 2 years) Washout: 4-week no treatment Phase 3: 48-weeks on the Phase 1 assigned treatment (total 3 years) Phase 4: Subjects could continue for a 4th year of treatment. *Country:* UK *Duration:* Long term (open-ended). *Inclusion criteria:* patients with mild to moderate AD (DSM IV dementia of AD type), with or without a coexisting diagnosis of vascular dementia. *Assessments:* Multiple, throughout study	1. donepezil (5mg/day 12 week run-in period, followed by Phase 1: 5-10mg/day, Phase 2: 5 or 10mg/day, Phase 3: 5 or 10mg/day) n=282 (at 12 week run-in period) 2. placebo n=283 (at 12 week run-in period) n= 565 patients randomised *Age range*: 46-93 (median: placebo 76, donepezil 75)	*Primary* Progression of disability on BADLs, Entry to institutional care *Secondary* BADL, MMSE, NPI, GHQ, *Safety and tolerability* Adverse events
Sub-analysis of caregiver data of a 1 year study of donepezil vs. placebo in mild to moderate AD (Wimo 2004) Full study: DON-NY-96-001 (reported in original	To investigate the change in caregiver time burden over 1 year for caregivers of patients with mild to moderate AD, and the impact of donepezil treatment on this burden.	RCT, DB, placebo-controlled, Multicentre study. *Country:* Denmark, Sweden, Finland and the Netherlands. *Duration:* 52-weeks *Inclusion criteria:* patients with mild to moderate AD (MMSE 10-26). *Assessments:* baseline, weeks 12, 24, 36, and 52.	For this sub-analysis, only data from those caregivers actively (>0 hr/day) providing care to the AD patient at study baseline were included: 1. donepezil 5 or 10mg/day (n=96) 2. placebo (n=94) *Age range*: not reported for patients in this sub-analysis.	*Primary* RUD

Study Name	Objective(s)	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
company submission) (Winblad 2001)				
Direct Comparator RCTs				
Long-term (2 year) donepezil or rivastigmine in moderate to severe AD (Bullock 2005)	To evaluate the efficacy and tolerability of donepezil and rivastigmine in patients with moderate to moderately severe AD over a two-year period.	RCT, DB, parallel group, Multicentre study. *Country:* Multinational *Duration:* 24-months *Inclusion criteria:* patients with moderate to moderately severe AD (MMSE 10-20), with or without symptoms suggestive of Lewy body dementia. *Assessments:* baseline, 'regular intervals' up to study end at week 104.	1. donepezil 5 or 10mg/day during 16 week titration period, followed by up to 10 mg/day thereafter (n=499) 2. rivastigmine 3-12mg/day during 16 week titration period, followed by up to 12 mg/day thereafter (n=495) n=998 patients randomised *Age range*: 50-85 years (mean 76)	*Primary* SIB *Secondary* ADCS-ADL, GDS, MMSE, NPI *Safety and tolerability* Adverse events, treatment related adverse events, discontinuations due to adverse events, vital signs
Sub-analysis of Bullock 2005: Efficacy in patients with versus without symptoms suggestive of concomitant Lewy Body disease (Touchon 2006)	Retrospective analysis to investigate whether patients with and without symptoms suggestive of Lewy body disease demonstrate different responses to therapy.	Retrospective sub-analysis of above study (Bullock 2005).	1. donepezil treated patients with symptoms of Lewy body disease (n=24) 2. donepezil treated patients without symptoms of Lewy body disease (n=475) 3. rivastigmine treated patients with symptoms of Lewy body disease (n=25) 4. rivastigmine treated patients without symptoms of Lewy body disease (n=470)	*Primary* SIB *Secondary* ADCS-ADL, GDS, MMSE, NPI *Safety and tolerability* Adverse events, discontinuations due to adverse events, vital signs
Sub-analysis of Bullock 2005: Effect of age on response to rivastigmine and donepezil (Bullock 2006)	Retrospective analysis to investigate whether younger and older patients showed differential tolerability and efficacy responses to therapy.	Retrospective sub-analysis of above study (Bullock 2005).	1. donepezil treated patients < 75 years (n=185) 2. donepezil treated patients ≥ 75 years (n=314) 3. rivastigmine treated patients < 75 years (n=177) 4. rivastigmine treated patients ≥ 75 years (n=318)	*Primary* SIB *Secondary* ADCS-ADL, GDS, MMSE, NPI-10 *Safety and tolerability* Adverse events, discontinuations due to adverse events, vital signs

Study Name	Objective(s)	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
Randomised, placebo-controlled study of memantine on top of stable donepezil treatment				
Memantine treatment in patients with moderate to severe AD already receiving donepezil (Tariot 2004)	To determine the efficacy and safety of memantine in patients with moderate to severe AD already recieving stable treatment with donepezil.	RCT, DB, parallel group, Multicentre study. *Country:* US *Duration:* 24-weeks *Inclusion criteria:* patients with moderate to severe AD (MMSE 5-14), who were receiving donepezil (for > 6 months before entrance to study and at a stable dose 5 of 10mg/day) for ≥ 3 months. *Assessments:* baseline, Weeks 4, 8,12,18 and 24.	All patients maintained on donepezil 5 or 10 mg/day for the duration of the study. 1. memantine (5 mg/day titrated to 20 mg/day) (n=203) 2. placebo(n=201) n= 404 patients randomised *Age range*: at least 50 years (mean 76)	*Primary* SIB, ADCS-ADL *Secondary* CIBIC-Plus, NPI, BGP *Safety and tolerability* Adverse events, treatment related adverse events, discontinuations due to adverse events, laboratory tests, ECG, vital signs.
Exploratory reanalysis of Tariot 2004: Cognitive response (Schmitt 2006)	Exploratory reanalysis to investigate the effects of memantine in patients already recieving stable donepezil on **cognition.**	Exploratory reanalysis of above study (Tariot 2004).	As above (Tariot 2004)	*Primary* SIB individual items, SIB domains, SIB higher-order subscales
Exploratory reanalysis of Tariot 2004: Activities of Daily Living (Feldman 2006)	Exploratory reanalysis to investigate the effects of memantine in patients already recieving stable donepezil on **activities of daily living.**	Exploratory reanalysis of above study (Tariot 2004).	As above (Tariot 2004)	*Primary* ADCS-ADL individual items, ADCS-ADL subscales
Exploratory reanalysis of Tariot 2004: Behavioural effects (Cummings 2006)	Exploratory reanalysis to investigate the effects of memantine in patients already recieving stable donepezil on **behaviour.**	Exploratory reanalysis of above study (Tariot 2004).	As above (Tariot 2004)	*Primary* NPI domains, NPI-CDS

Study Name	Objective(s)	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
Prospective longitudinal studies				
Efficacy and safety of donepezil over 3 years, an open label, multicentre study in patients with AD (Burns 2007)	To assess the long-term efficacy and safety of donepezil in patients with mild to moderate AD who had previously participated in a 24-week double-blind study.	Prosepctive, Open-label extension, Multicentre study. Phase 1: 24-week RCT, DB, placebo controlled (donepezil 5-10mg, or placebo, followed by 6-week SB placebo washout (EO44-304, reported in original submission). **Phase 2: 132-week open-label extension. Patients received donepezil (6 weeks- 5mg, followed by 10 mg for remainder of study). (Open-label extension study reported in current submission).** *Country:* Multinational *Duration:* 132- weeks *Inclusion criteria:* patients with mild to moderate AD (open-label phase baseline MMSE score 10-26) who completed the DB phase. *Assessments:* baseline (termination of Phase 1), weeks 6, 12, and at 12-week intervals thereafter, up to week 132.	n= 579 patients. Open label extension: donepezil 5mg/day for 6 weeks, followed by 10mg/day thereafter (n=579) *Age range*: 51–91 (mean 71)	*Primary* ADAS-cog, CDR-SB *Secondary* IDDD QoLS *Safety and tolerability* Adverse events, treatment related adverse events, discontinuations due to adverse events
Swedish Alzheimer Treatment Study (SATS) (Wallin 2007)	To evaluate the long-term effects of donepezil treatment in patients with AD in a routine clinical setting.	Prospective, Multicentre, Observational study. *Country:* Sweden *Duration:* 3-years *Inclusion criteria:* patients with AD (mean MMSE score 22.0, no inclusion range specifed) and not taking AChEIs prior to baseline *Assessments:* baseline, 8 weeks, every 6 months up to 3 years.	n= 435 patients receiving donepezil 1. patients receiving donepezil 5mg/ day for 4-8 weeks, followed by up to 10 mg/day (n=435). *Age range:* at least 40 years (mean 75)	*Primary Outcome* MMSE, ADAS-cog, CIBIC, IADL *Safety and tolerability* Discontinuations due to adverse events

Study Name	Objective(s)	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
Sub-analysis of SATS study (Wallin 2007): Changes in cognitive domains during three years in patients with AD treated with donepezil . (Persson 2009)	To identify salient cognitive domains in the standard assessment tools MMSE and ADAS-cog and describe patterns of decline within these domains in AD patients receiving donepezil for 3 years. Secondary aim to identify clinically relevant differences between 3-year completers and patients who dropped out before study end.	Sub-analysis of above study (Wallin 2007).	1. patients receiving donepezil 5mg/ day for 4-8 weeks, followed by up to 10 mg/day (n=421 included in sub-analysis - 14 subjects excluded due to missing values).	*Primary Outcome* MMSE, ADAS-cog, Factor analyses and construction of cognitive domains

Abbreviations: AD: Alzheimer's Disease; **DB**: double-blind; **RCT**: randomised controlled trial.
ACDS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; **ADAS-cog:** Alzheimers' Disease Assessment Scale Cognitive Sub-scale; **BADL:** Bristol Activities of Daily Living Scale; **BGP**: Behavioural Rating Scale for Geriatric Patients; **CDR-SB**: Clinical Dementia Rating – Sum of the Boxes; **CGIC:** Clinical Global Impression of Change; **CIBIC:** Clinician's Interview Based Impression of Change; **CIBIC-Plus:** Clinician's Interview Based Impression of Change Plus version; **CMAI:** Cohen-Mansfield Agitation Inventory; **GDS:** Global Deterioration Scale; **GHQ:** General Health Questionnaire; **IADL:** Instrumental Activities of Daily Living; **IDDD:** Interview for Deterioration of Daily Living Activities in Dementia; **MMSE:** Mini Mental State Examination; **SIB:** Severe Impairment Battery; **NPI:** Neuropsychiatric Inventory; **NPI-10:** Neuropsychiatric Inventory-10 domains; **NPI-CDS**: Neuropsychiatric Inventory – Caregiver Distress Scale; **QoLS:** Quality of Life Scale; **RUD:** Resource Utilisation in Dementia.

2.3.3.1 Quality of the Research

All RCTs identified in the review were evaluated to determine the quality of the trials according to NICE Centre for Reviews and Dissemination (CRD) report No. 4 (see NICE CRD, Appendix C) (Table 2). They were critically appraised for relevance, validity, and minimisation of bias and whether the results are important for answering the research questions in the study. A number of rules for describing the qualities of RCTs were specified prior the literature review (Appendix C). Note that as the Wimo (2004) study is a subanalysis of the Nordic study (Winblad et al., 2001) included in the 2001 submission, a quality assessment is not included here.

Table 2. Quality Assessment Table for Donepezil RCTs

Author, Year	Number of patients randomized	How was allocation concealed?	Which randomization technique was used?	Was a justification of the sample size provided?	Was follow-up adequate?	Were all assessors blinded to treatment allocation?	Were all care providers blinded?	Was the design parallel or crossover? (parallel=yes; crossover=no)	If crossover, is there risk of carry-over affect?	Was the method of concealment presented?	Are dosage regimens within those cited in the SmPC?	Were all groups similar at baseline in terms of prognostic factors?	Were the statistical analyses used appropriate?	Was the intent to treat population used?	Were there any confounding factors that may attenuate the interpretation of the
Bullock et. al. 2006 Bullock et. al. 2005 Touchon et. al. 2006	998	All personnel involved in the conduct of study are unaware of the treatment groups	Stratified randomization and Interactive Voice Response System generated randomization numbers	YES	YES	YES	YES	YES	N/A	YES	YES	YES	YES	YES	NO
Courtney et. al. 2004*	565	NR	NR	YES	YES	YES	YES	YES	N/A	NR	YES	YES	YES	NR	NO
Tariot et. al. 2004 Cummings et. al. 2006 Feldman et. al. 2006 Schmitt et. al. 2006	404	NR	Permuted blocks of 4 according to the biostatistics department generated randomization list	YES	YES	YES	YES	YES	N/A	NO	YES	YES	YES	YES	NO

NR, not reported; [1]15-week trial; [2]24-week trial; †one arm given dose at 1mg/qd, which is not an approved dose according to SmPC for donepezil

*Please see additional comments below

The AD2000 study (Courtney, 2004) is not fit for purpose. Its methodological limitations have previously been highlighted by Eisai/Pfizer in response to the NICE revised Final Appraisal Decision of 2006 and by the wider research community (see for example, Birks 2006). These limitations include the following serious deficiencies in design and statistical analysis:

- The study was under-powered; it set out to recruit 2000 patients but only recruited 565. It therefore had insufficient patients to carry out the probability calculations necessary to determine the statistical significance of the trial's outcomes.
- The treatment design (i.e. multiple washout periods) does not reflect current medical practice. Indeed, data have shown that patients who stop treatment for a short period lose their initial treatment benefit (Doody 2001 (reported in original submission); Burns 2007 (reported in current submission)). The design of this study renders it unsuitable for pooling with other donepezil studies.
- Entry criteria were based upon an "uncertainty principle" which was biased in favour of patients who were unlikely to respond to donepezil.
- The study population was mixed (i.e. it included patients with non-AD dementia).

Therefore, although we have included this study here for completeness and transparency, we feel that it does not merit consideration in the appraisal of donepezil.

2.3.3.2 Placebo-controlled RCTs of Donepezil

Table 3 below summarises the efficacy results from the RCTs identified in the current literature search along with those from the 2001 and 2004 submissions which are included for comparison purposes. The efficacy results are presented according to outcome domain.

Table 3. A Summary of RCT Efficacy Results (on Measures of Cognition, Function, Behaviour, Issues Pertaining to the Caregiver, and to Institutionalisation

				Outcome Measures					
Study (refs)	**AD severity at baseline (MMSE range)**	**Duration of double-blind period (weeks)**	**No. subjects per treatment group**	**Cognition**	**Function**	**Behaviour**	**Global**	**Caregiver Issues**	**Time to/risk of Institutionalisation**
New RCTs (and sub-analyses of existing RCTs) Identified in Current Literature Search									
AD2000 Long term donepezil in mild to moderate AD Courtney 2004	Mild to moderate (10-26)	DB, 4-Phase study with washout periods. Run-in: 12 P1: 48 W/O: 6 P2: 48 W/O: 4 P3: 48 P4: could continue for 4th yr.	Randomised and treated first 60 weeks Placebo: 244 Donepezil 5 or 10 mg: 242 (first 60 weeks of study)	+ (MMSE)	NS (12 weeks + > 12 weeks BADL) **NS: progression of disability on BADLs**	NS (NPI)	*Not measured*	NS (GHQ for carers' psychological morbidity)	NS
Sub-analysis of caregiver data from Nordic Study Wimo 2004	Mild to moderate (10-26)	52	Placebo: 144 Donepezil 5 or 10mg: 142	*Not measured*	*Not measured*	*Not measured*	*Not measured*	**+ (RUD)**	*Not measured*
RCTs in 2004 Submission									
DON-NY-96-002-324 **MSAD** Feldman 2001 Feldman 2003	Moderate to moderately severe (5-17)	24	Placebo: 146 Donepezil 5 or 10mg: 144	+ (S-MMSE) + (SIB)	+ (DAD) + (IADL+) + (PSMS+)	+ (NPI-12)	**+ (CIBIC-**Plus)	+ (CSS) + (CD) NS (HRQoL of caregivers)	*Not measured*
E2020-A001-402 **MILD AD** Seltzer 2004	Mild (21-26)	24	Placebo: 57 Donepezil 5 or 10mg: 96	**+ (ADAS-cog)** + (MMSE)	*Not measured*	NS (Apathy)	NS (CDR-SB)	NS (HRQol)	*Not measured*

				Outcome Measures					
DON-DK-98-001 **AWARE** Johannsen 2006	Mild to moderate (10-26)	12	Placebo: 103 Donepezil 10mg: 99	**NS (ADAS-cog)** + (MMSE)	NS (DAD)	+ (NPI)	*Not measured*	*Not measured*	*Not measured*
Neuropsychiatric Symptom Study Holmes 2004	Mild to moderate (10-26) Neuropsychiatric symptoms (NPI > 11)	12	Placebo: 41 Donepezil 5 or 10mg: 55	+ (MMSE; both double-blind and open-label phases)	*Not measured*	**+ (NPI; both double-blind and open-label phases)**	*Not measured*	+ (NPI-CDS)	*Not measured*
RCTs in 2001 Submission									
A001-201 **US Phase II study** Rogers 1996	Mild to moderate (10-26)	12	Placebo: 40 Donepezil 1mg: 42 Donepezil 3mg: 40 Donepezil 5mg: 39	+ (ADAS-cog) NS (MMSE)	*Not measured*	*Not measured*	NS (CGIC) NS (CDR-SB at week 6)	*Not measured*	*Not measured*
A001-301 **Pivotal US Phase III study** Rogers 1998a	Mild to moderate (10-26)	12	Placebo: 54 Donepezil 5mg: 157 Donepezil 10mg: 158	+ (ADAS-cog) + (MMSE)	*Not measured*	*Not measured*	+ (CIBIC-Plus) + (CDR-SB)	*Not measured*	*Not measured*
A001-302 **Pivotal US Phase III study** Rogers 1998b	Mild to moderate (10-26)	24	Placebo: 162 Donepezil 5mg: 154 Donepezil 10mg: 157	+ (ADAS-cog) + (MMSE)	*Not measured*	*Not measured*	+ (CIBIC-Plus) + (CDR-SB)	*Not measured*	*Not measured*
EO44-304 **Multi-national Phase III study** Burns 1999	Mild to moderate (10-26)	24	Placebo: 274 Donepezil 5mg: 271 Donepezil 10mg: 273	+ (ADAS-cog)	NS (IDDD-B) + (IDDD-C)	*Not measured*	+ (CIBIC-Plus) + (CDR-SB)	*Not measured*	*Not measured*
DON NY-96-001 **A multinational study. The Nordic Study**	Mild to moderate (10-26)	52	Placebo: 144 Donepezil 5 or 10mg: 142	+ (MMSE)	NS (IADLs) + (PSMS) + (PDS)	NS (NPI)	+ (GBS)	*Not measured*	*Not measured*

			Outcome Measures						
Winblad 2001									
A001-312 **A US study. The Functional Survival Study** Mohs 2001	Mild to moderate (12-20)	54	Placebo: 217 Donepezil 5 or 10mg: 213	+ (MMSE)	+ (ADFACS)	*Not measured*	+ (CDR)	*Not measured*	*Not measured*
A001-311 **A US study. The Nursing Home Study** Tariot 2001	Mild to severe (5-26) Nursing home residents	24	Placebo: 105 Donepezil 5 or 10mg: 103	+ (MMSE)	NS (PSMS)	NS (NPI-NH-10) + (agitation/aggression items)	+ (CDR-SB-NH)	*Not measured*	*Not measured*

+ indicates that results for that outcome measure were statistically significant in favour of donepezil vs. placebo (for all doses of donepezil used in study unless otherwise stated). NS denotes no significant difference between donepezil vs. placebo. 'Not measured' signifies where a tool was not measured. The name of the relevant tool is given in brackets. Entries in bold denote primary outcome measures for that study.

AD: Alzheimer's Disease; AWARE: Aricept Washout and Rechallenge study; DB: double-blind; MSAD: Moderately Severe Alzheimer's Disease study; P1: Phase 1; RCT: randomised controlled trial; W/O: washout period with no study treatment.

Outcome measures:

***Cognition*: ADAS-cog**: Alzheimer's' Disease Assessment Scale Cognitive Sub-scale; **MMSE**: Mini Mental State Examination; **S-MMSE**: Standardised Mini Mental State Examination, **SIB:** Severe Impairment Battery**.**

***Function*: ADFACS**: Alzheimer's' Disease Functional Assessment and Change Scale; **BADL:** Bristol Activities of Daily Living Scale; **DAD**: Disability Assessment for Dementia; **IADL**: Instrumental Activities of Daily Living, **IADL+:** modified Instrumental Activities of Daily Living**; IDDD-B**: Interview for Deterioration of Daily Living Activities in Dementia Basic Task score; **IDDD-C**: Interview for Deterioration of Daily Living Activities in Dementia Complex Task score; PDS: Progressive Deterioration Scale; **PSMS**: Physical-Self Maintenance Scale; **PSMS+**: modified Physical-Self Maintenance Scale.

***Behaviour*: CMAI:** Cohen-Mansfield Agitation Inventory; **NPI**: Neuropsychiatric Inventory; **NPI-12**: Neuropsychiatric Inventory-12 domains; **NPI-NH-10**: Neuropsychiatric Inventory – Nursing Home Version- 10 domains.

***Global*: CDR**: Clinical Dementia Rating; **CDR-SB**: Clinical Dementia Rating – Sum of the Boxes; **CDR-SB-NH**: Clinical Dementia Rating – Sum of the Boxes **CGIC**: Clinical Global Impression of Change; **CIBIC-Plus**: Clinician's Interview Based Impression of Change – plus version; **GBS**: Gottfries, Brane and Steen Scale.

***Caregiver Issues*: CD**: Caregiver Dairy; **CSS**: Caregiver Stress Scale; **GHQ**: General Health Questionnaire; **HRQoL**: Health Related Quality of Life; **NPI-CDS**: Neuropsychiatric Inventory – Caregiver Distress Scale**; RUD**: Resource Utilisation in Dementia.

2.3.3.2.1 Effects of Donepezil on Cognition

Table 3 above demonstrates that all 12 RCTs (range 12-54 weeks; MMSE 5-26) from the previous and current submissions that report on the domain of cognition (using the ADAS-cog, MMSE or SIB scales) found a statistically significant advantage for donepezil versus placebo; with four of these reporting a statistically significant difference on two different cognitive scales. It is of note that in the only RCT of an AChEI in an exclusively mild patient population, donepezil demonstrated a statistically significant advantage vs. placebo on ADAS-cog and MMSE.

2.3.3.2.2 Effects of Donepezil on Function

Of seven RCTs reporting on the function domain, four reported a statistically significant difference favouring donepezil versus placebo on at least one scale, while the other three reported non-significant trends in favour of donepezil. In addition, a recently published meta-analysis of seven donepezil RCTs found a statistically significant advantage favouring donepezil versus placebo on the function domain (Hansen, 2008).

2.3.3.2.3 Effects of Donepezil on Behaviour

Seven studies from these submissions investigated the effects of donepezil on the behavioural symptoms of AD (12-52 weeks; MMSE 5-26); three of these found a statistically significant difference between donepezil and placebo on the NPI, with a fourth study (the Nursing Home Study; Tariot et al., 2001) finding a statistically significant difference in the items measuring agitation/aggression, although not on total NPI score. Positive effects on behaviour seen in the MSAD study (Feldman et al., 2001;2003) are also reflected by the statistically significant positive effects of donepezil compared with placebo on caregiver diary assessments in that study. The caregiver diary provides the caregiver's rating, in comparison to baseline, of the patient's social behavior based on the components of social interaction, engagement and interest in conversation, and initiation of pleasurable activities.

2.3.3.2.4 Effects of Donepezil on Global Function

Global function (CIBIC-Plus, CDR-SB or GBS) is measured in nine of the studies presented in these submissions (12-54 weeks; MMSE 5-26) with statistically significant results in favour of donepezil in seven of them.

2.3.3.2.5 Effects of donepezil on the caregiver

Few RCTs to date have evaluated the effect of donepezil on the caregiver. However, two studies in the 2004 submission (Feldman et al., 2001, 2003; Holmes et al., 2004) report positive effects of donepezil on levels of caregiver stress. In the MSAD study (Feldman et al., 2001, 2003), in patients with moderate to moderately severe disease, 24 weeks of treatment with donepezil had a statistically significant effect on levels of caregiver stress, compared with placebo. In the Holmes (2004) study, where patients are randomised to double-blind treatment with either donepezil or placebo following 12 weeks open label treatment with donepezil, patients randomised to placebo showed a significant worsening of

neuropsychiatric symptoms and a worsening of caregiver distress at both 6 and 12 weeks post-randomisation compared with a continued improvement in those who remained on donepezil treatment.

In a sub-analysis of the Nordic study, a one-year, multicentre, placebo-controlled RCT of donepezil, Wimo et al. (2004) found a significant difference in favour of donepezil on the Resource Utilization in Dementia (RUD). At the end of one year of treatment, the caregivers of placebo patients were spending 106.8 minutes more each day providing care than they had at baseline while the caregivers of donepezil patients were providing 42.6 minutes more each day than at baseline, a statistically significant difference ($p = 0.03$). This study is an important addition to the evidence base as the ability of donepezil to improve caregiver outcomes is maintained after one year of treatment.

2.3.3.3 Head to Head Drug Comparisons

While all three licensed AChEIs have demonstrated significant benefits in the domains of cognition, function and behaviour, there have been few studies that directly compare them. One such comparator RCT met the inclusion criteria for this submission (Bullock, 2005; Table 1). This two-year prospective, multicentre, double blind, parallel-group RCT compared the efficacy and tolerability of donepezil 5 or 10 mg daily and rivastigmine capsules 3-12 mg daily in 998 patients with moderate to moderately severe probable AD (Table 4) and was powered to detect a difference in efficacy between both compounds. However, it failed to meet its primary endpoint. In addition, there was a higher rate of discontinuations in the rivastigmine compared with the donepezil treatment arms which may result in an overestimation of the benefit of rivastigmine in the LOCF intent to treat (ITT) analysis. Moreover, an independent Cochrane review (Birks et al., 2006) has concluded that in this study, there is no significant difference between donepezil and rivastigmine in their effects on cognitive function, activities of daily living and behavioural disturbance and global assessment as measured by the Global Deterioration Scale (GDS). In a previous comparator study of rivastigmine and donepezil, similar discontinuation rates were observed (Wilkinson, 2002). Hence, it can be assumed that the magnitude of clinical effect is similar across the AChEI class.

Table 4. Summary of Efficacy in Direct Comparator RCTs (Current Search and 2004 Submission)

New Comparator RCT Identified in Current Literature Search								
				Cognition		Function	Behaviour	Global
Study/ Refs	**Methods**	**AD severity at baseline (MMSE range)**	**Number of subjects per treatment group**	**MMSE**	**SIB**	**ADL (ACDS- ADL)**	**NPI**	**GDS**
FULL STUDY	2-year, RCT, DB, parallel-group multicentre study. Donepezil: 5 mg/day (Weeks 1-8); 10 mg/day (Weeks 9-16) Rivastigmine: started at 3 mg/day and increased by 3 mg/day every 4 weeks to 12 mg/day. After titration, dose maintained at the highest tolerated level for the remainder of the 2 years.	Moderate to severe (10-20) with or without Lewy Body Disease	Donepezil 5 or 10mg/day: 499 Rivastigmine 3-12mg/day: 495	**FULL STUDY ANALYSIS**				
Long term (2 year) Donepezil vs. Rivastigmine (Bullock 2005)				NS	NS	+ favours rivastigmine	NS	+ favours rivastigmine
SUB ANALYSIS				**SUB ANALYSIS**				
Efficacy in patients with vs. without Lewy Body disease (Touchon 2006)				**Patients <u>with</u> Lewy Body Disease**				
				+ favours rivastigmine	+ favours rivastigmine	+ favours rivastigmine	NS	NS
				Patients <u>without</u> Lewy Body Disease				
				NS	NS	+ favours rivastigmine	NS	NS
SUB ANALYSIS				**SUB ANALYSIS**				
Effect of age on response to donepezil or rivastigmine disease (Bullock 2006)				**Patients < 75 years of age**				
				NS	NS	+ favours rivastigmine	+ favours rivastigmine	+ favours rivastigmine
				Patients ≥ 75 years of age				
				NS	NS	NS	NS	NS
Comparator RCTs Reported in 2004 Submission								

				Cognition		Physician Satisfaction/Ease of Use Questionnaire	Caregiver Satisfaction/Ease of Use Questionnaire
				MMSE	ADAS-cog		
Study DON-CH-98-001 Donepezil vs. rivastigmine (Wilkinson 2002)	12-week, RCT, Open-Label, multicentre study. Patients treated with either donepezil (5 or 10mg/day or rivastigmine 1.5-6mg BD.	Mild to moderate (10-26)	Donepezil 5 or 10 mg/day: 56 Rivastigmine 1.5-6mg BD: 55	NS	NS	+ favours donepezil	+ favours donepezil
Study E2020-A001-407 Donepezil vs./ galantamine (Jones 2004)	12-week, RCT, Open-Label, multicentre study. Patients treated with either donepezil (5 or 10mg/day or galantamine 4-12mg BD.	Mild to moderate (10-24)	Donepezil 5 or 10 mg/day: 64 Galantamine 4-12mg BD: 56	+ favours donepezil	+ favours donepezil	+ favours donepezil	+ favours donepezil

+ indicates that results for that outcome measure were statistically significantly different between comparators.
NS denotes no significant difference between donepezil vs. comparator.
BD: twice daily; DB: double blind.
ACDS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; ADAS-cog: Alzheimer's' Disease Assessment Scale Cognitive Sub-scale; ADL: Activities of Daily Living; GDS: Global Deterioration Scale; MMSE: Mini Mental State Examination; NPI: Neuropsychiatric Inventory; SIB: Severe Impairment Battery

2.3.3.4 Combination Therapy: Memantine Added to Stable Donepezil Treatment

Besides the three AChEIs (donepezil, rivastigmine and galantamine), memantine is the only other agent approved in the UK for the symptomatic treatment of AD. Memantine is a low to moderate affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist, and therefore belongs to an entirely different chemical class to the AChEIs. Because of their differing mechanisms of action combination therapy involving memantine and an AChEI has been investigated.

Our clinical effectiveness literature search identified one study of memantine added on top of stable donepezil therapy (Tariot et al., 2004; along with three sub-analyses, Cummings et al., 2006; Schmitt et al., 2006; Feldman et al., 2006) (Table 5). Although this is a double-blind, placebo-controlled RCT of memantine, and therefore cannot be used to demonstrate the efficacy of donepezil, nonetheless we include it here because it demonstrates the efficacy and safety of combination treatment and supports a treatment strategy in which donepezil therapy is continued and memantine is added.

In patients with moderate to severe AD who had received donepezil for more than six months, and at a stable dose (5-10 mg/day) for at least three months before entrance to the double-blind study, addition of memantine to donepezil resulted in statistically significant benefits on measures of cognition, activities of daily living, behaviour and global outcome, compared with donepezil plus placebo at endpoint (Table 5). Indeed, for 12 weeks after initiating memantine therapy on top of donepezil, improvements in cognitive scores were observed. Sub-analysis of the individual NPI domains found significant effects in favour of memantine plus donepezil on agitation/aggression, eating/appetite and irritability/lability (Cummings et al., 2006). These studies provide strong evidence for the benefit of adding memantine therapy to stable donepezil therapy.

Table 5. Summary of Efficacy of Memantine Treatment in Patients with Moderate to Severe AD Receiving Stable Donepezil Treatment

				Cognition	Function		Behaviour	Global
Study/Refs	**Methods**	**AD severity at baseline (MMSE range)**	**Number of subjects per treatment group**	**SIB**	**ACDS- ADL**	**CIBIC-Plus**	**NPI**	**BGP**
FULL STUDY **Memantine treatment in patients with moderate to severe AD already receiving donepezil** (Tariot 2004)	24-week, RCT, DB, parallel-group multicentre study. All patients maintained on donepezil 5 or 10 mg/day for the duration of the study.	Moderate to severe (5-14) receiving donepezil 5 or 10 mg/day for the study duration.	Memantine 5 mg/day titrated to 20 mg/day: 203 Placebo: 201	**FULL STUDY ANALYSIS** +	+	+	+	+
Sub-ANALYSIS **Exploratory reanalysis: Cognitive response** (Schmitt 2006)				**EXPLORATORY REANALYSIS (Cognition)** **SIB individual items:** + Recalling examiner's name + Confrontation naming- cup + Showing how to use a cup with photographic prompt + Showing how to use a cup with an actual cup + Showing how to use a spoon with an actual spoon			**SIB domains:** + Memory + Language + Praxis	
Sub-ANALYSIS **Exploratory reanalysis: Activities of Daily Living** (Feldman 2006)				**EXPLORATORY REANALYSIS (Function)** **ADSL-ADL individual items:** + Grooming + Toileting + Conversing + Watching television + Being left alone			**ADCS-ADL subscales:** + Higher level functions + Connectedness/autonomy	
Sub-ANALYSIS **Exploratory reanalysis: Behavioural effects** (Cummings 2006				**EXPLORATORY REANALYSIS (Behaviour)** **NPI domains:** + Agitation/aggression + Irritability/lability + Appetite/eating changes			**NPI-CDS total:** NS **NPI-CDS domains:** + Agitation/aggression + Night-time behaviour + Appetite changes	

+ indicates that results for that outcome measure were statistically significant in favour of donepezil/memantine vs. donepezil/placebo.
NS denotes no significant difference between donepezil/memantine vs. donepezil/placebo.
Abbreviations: AD: Alzheimer's Disease; DB: double-blind; RCT: randomised controlled trial; ACDS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; BGP: Behavioural Rating Scale for Geriatric Patients; CIBIC-Plus: Clinician's Interview Based Impression of Change Plus version; MMSE: Mini Mental State Examination; NPI: Neuropsychiatric Inventory; NPI-CDS: Neuropsychiatric Inventory – Caregiver Distress Scale. SIB: Severe Impairment Battery.

2.3.4 Evidence from Prospective Longitudinal Studies

In addition to identifying relevant RCTs, the literature search also focused on identifying prospective longitudinal studies of more than two years duration in order to capture important longer-term efficacy and safety data. The criterion of at least two years study duration was selected as an inclusion criterion since it was recognised that RCT data of up to two years was already available for donepezil (Bullock, 2005) and so observational data was identified to complement this evidence base. This strategy yielded two prospective donepezil studies with duration in excess of two years (Burns, 2007; Wallin, 2007). The main efficacy and safety findings from these studies is presented in Table 6, followed by a summary description of the implications for longer-term use of donepezil in AD patients. Note that a sub-analysis of the study by Wallin and co-workers was identified in our clinical effectiveness literature search (Persson 2009). This sub-analysis analysed the process of decline within separate cognitive domains of the MMSE and ADAS-cog (general, memory and spatial). It found that the course of illness in the three domains was heterogeneous, but no clinically relevant correlates of this heterogeneity could be identified. A summary of this study can be found in Appendix E but as its findings do not contribute to the evidence base for donepezil it has not been included in Table 6.

Table 6. Prospective Longitudinal Studies with a Duration of > 2 years Reported in Current Submission

				Cognition		Function			Global	
Study/ Refs	**AD severity at baseline (MMSE range)**	**Study design, duration**	**Number of subjects per treatment group**	**MMSE**	**ADAS-cog**	**CIBIC**	**IADL**	**ADL (IDDD)**	**CDR-SB**	**QoLS**
Efficacy and safety of donepezil over 3 years Burns 2007	Mild to moderate (10-26) Patients had completed 24-week, DB, placebo controlled RCT, followed by 6-week washout (E044-304, reported in original submission)	Phase 1: DB, RCT 24-week 6-week washout Phase 2: Open-Label ext: 132-weeks	Donepezil 5/10mg: 579	not measured	DB phase + Washout phase Worsens Open-Label Improve up to 24 weeks.	not measured	not measured	DB phase not reported Washout phase not reported Open-Label Maintain over first 24 weeks	DB phase + Washout phase Worsens Open-Label Improve up to 12 weeks.	DB phase not reported Washout phase not reported Open-Label Improve up to 12 weeks
Swedish Alzheimer Treatment study- 3 years Wallin 2007	No inclusion MMSE range specified	Prospective, Observational 3-year study	Donepezil 5/10mg: 435	Improved up to 6 months Declined below baseline by 3 years. Slower decline than predicted by historical controls or the Stern equation.	Worsened	Change from baseline: 6.2 over 3 years	Change from baseline: 5.1 over 3 years	not measured	not measured	not measured

+ indicates that results for that outcome measure were statistically significant in favour of donepezil vs. placebo (for all doses of donepezil used in study unless otherwise stated).
NS denotes no significant difference between donepezil vs. placebo.
'*Not measured*' signifies where a tool was not used.
MMSE: Mini Mental State Examination; ADAS-cog: Alzheimer's' Disease Assessment Scale Cognitive Sub-scale; CIBIC: Clinician's Interview Based Impression of Change; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living; IDDDD: Interview for Deterioration of Daily Living Activities in Dementia; CDR-SB: Clinical Dementia Rating - Sum of Boxes; QoLS: Quality of Life Scale.

The open-label extension study of a 24-week randomised, placebo-controlled study, in which patients received donepezil (5 or 10 mg daily) for up to 132 weeks (Burns, 2007) confirms and extends the results of earlier RCTs and open-label studies, in demonstrating that donepezil improves cognition and global function. The difference in mean ADAS-cog score from the beginning of double-blind treatment to the end of follow-up was approximately 15 points. As several long term studies have indicated that annual decline in ADAS-cog in untreated AD patients is approximately 11 points per year (Stern et al., 1994; Farlow et al., 2003; Suh et al., 2004) a change of 30 ADAS-cog points would be expected in untreated AD patients over a 3-year period. Hence, the rate of cognitive deterioration in these patients treated with donepezil is less than would be expected had they been untreated. Thus, the cognitive benefits of donepezil in patients with mild to moderate AD appear to be maintained for up to three years. This conclusion is supported by the results of a three-year prospective observational study of patients receiving donepezil in a routine clinical setting (Wallin, 2007). In these patients, the mean MMSE score remained improved relative to baseline for more than six months and the MMSE change after three years was 3.8 points, less than expected from historical cohorts (6–12 points). After one year 50% of patients were considered unchanged or improved on their global assessment. After three years, this had dropped to 30%. These positive treatment effects could be the result of sustained long-term treatment with donepezil where there are no interruptions in the treatment regimen.

The Aricept Washout and Rechallenge (AWARE) (Johannsen et al., 2006), reported in the 2004 submission, provided a pivotal piece of evidence for the need for treatment maintenance. This was a 12 week double blind, placebo-controlled RCT in patients with mild to moderate AD (MMSE score 10-26 at baseline), who had not shown any apparent clinical improvement after a preliminary 12 to 24 weeks open label treatment with donepezil. The inclusion criterion for entry into the RCT was a classification of “no apparent clinical benefit” in the initial open-label phase. Patients randomised to receive further donepezil in the double-blind phase showed a significant improvement in cognition and behaviour and a trend to improvement in activities of daily living. Three quarters of patients treated continuously with donepezil showed statistically significant improvement compared with placebo over two or more of the domains of cognition, function and behaviour. The AWARE study shows that initial decline or stabilisation does not necessarily indicate a lack of efficacy of donepezil in AD.

2.4 Targeted Review of Observational Studies

The previous 2004 submission to NICE identified eight non-randomised and observational studies that focused on nursing home placement, early initiation of donepezil treatment, and use of donepezil in AD patients with co-morbid cerebrovascular disease. A brief summary of these studies can be found in Appendix F.

In addition to the new RCTs and prospective longitudinal studies identified in the present submission, the results of the literature search were also reviewed to identify donepezil-related AChEI observational studies of AD patients that addressed the following clinically important questions:

- **Is there any evidence of harm resulting from discontinuation of AChEIs at any stage of illness?**
- **Is there any observational evidence on caregiver burden for AChEIs as a class?**
- **Is there any benefit of continued use of AChEIs irrespective of severity in terms of prevention of increased use of anti-psychotics?**

This search identified three observational studies that addressed at least one of these questions. Burns et al (2007) has already been discussed in Section 2.3.4 above (see Table 1 and Table 6), but is also included here as it provides answers to one of the questions above. A summary of the study characteristics and the methods of each of these studies is presented in Table 7 below.

Table 7. Clinical Evidence for Donepezil: Observational Studies that Answer Clinically Important Questions

Study Name	Objective(s)	Related Publications	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
Efficacy and safety of donepezil over 3 years, an open label, multicentre study in patients with AD (Burns 2007)	To assess the long-term efficacy and safety of donepezil in patients with mild to moderate AD who had previously participated in a 24-week double-blind study.	Manuscripts Burns 2007: open label extension reported in current submission Burns 1999: phase 1 DB study, EO44-304, reported in original company submission	Prosepctive, Open-label extension, Multicentre study. Phase 1: 24-week RCT, DB, placebo controlled (donepezil 5-10mg, or placebo, followed by 6-week SB placebo washout (EO44-304, reported in original submission). **Phase 2: 132-week open-label extension. Patients received donepezil (6 weeks- 5mg, followed by 10 mg for remainder of study). (Open-label extension study reported in current submission).** *Country:* Multinational *Duration:* 132- weeks *Inclusion criteria:* patients with mild to moderate AD (open-label phase baseline MMSE score 10-26) who completed the DB phase. *Assessments:* baseline (termination of Phase 1), weeks 6, 12, and at 12-week intervals thereafter, up to week 132.	n= 579 patients. Open label extension: donepezil 5mg/day for 6 weeks, followed by 10mg/day thereafter (n=579) *Age range*: 51–91 (mean 71)	*Primary* ADAS-cog, CDR-SB *Secondary* IDDD QoLS *Safety and tolerability* Adverse events, treatment related adverse events, discontinuations due to adverse events
Effects of donepezil on neuropsychiatric symptoms in patients with mild to moderate AD and behavioural and psychological symptoms (Tanaka 2008)	To determine the efficacy and safety of 12-week open-label treatment with donepezil in patients with mild to moderate AD and 'behavioural and psychological symptoms of dementia' (BPSD), and to determine the effect of donepezil treatment on BPSD.	Manuscripts Tanaka 2008	Prospective, Multicentre, Observational study. *Country:* Japan *Duration:* 12-weeks *Inclusion criteria:* patients with mild to moderate AD (MMSE scores not reported) showing at ≥ one BPSD of hallucinations/delusions, wandering, and aggression. *Assessments:* baseline, 4, 8 and 12 weeks.	n= 252 patients. 1. patients receiving donepezil 3mg per day for up to 2 weeks, followed by 5 mg per day (n=252). *Age range:* none specified (mean 78)	*Primary Outcome* Changes in BPSD, HDS-R, MMSE, Caregiver's Burden *Safety and tolerability* Adverse events
Donepezil in AD: a clinical observational study evaluating individual	To assess the sensitivity of the Individual Symptom Score (IndiSS) to detect treatment benefits with donepezil in patients with	Manuscripts Reipe 2007	Prospective, Multicentre, Observational study. *Country:* Germany *Duration:* 6-months	n= 2046 (enrolled) 1. patients receiving donepezil 5mg/day for at least 1 month, followed by up to 10 mg/day	*Primary Outcome* IndiSS *Secondary Outcome* CGI, MMSE, DemTect *Safety and tolerability*

Study Name	Objective(s)	Related Publications	Design, Methods, Assessments	Study Treatments (Number of patients randomised, age range)	Outcome Measures (efficacy, safety and tolerability)
symptom scores (Riepe 2007)	mild to moderate AD in everyday life over 3 and 6 months.		*Inclusion criteria:* patients with mild to moderately severe AD (mean MMSE score 18.8, no inclusion range specifed) with or without concomitant cerebrovascular disease or Parkinsonian symptoms. *Assessments:* baseline, 3 and 6 months.	(n=2004) *Age range:* none specified (mean 75)	Adverse events, discontinuations due to adverse events
Effect of donepezil on mortality rates in nursing home placements with dementia (Gasper 2005)	To investigate whether donepezil treatment is associated with reduced mortality in nursing home residents who have dementia.	Manuscripts Gasper 2005	Retrospective, matched cohort, Observational study of residents of multiple nursing homes. 915,469 individuals from the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database were selected, which uses contains collected with the Minimum Data Set (MDS). *Country:* USA *Duration:* 2-years *Inclusion criteria:* nursing home residents with dementia, receiving donepezil (5 and 10 mg) who were not terminally ill at their initial MDS assessment, had consistent drug usage information, had information on the status of life or death by the end of follow up, and lived in a nursing home where at least 95% residents had consistently documented drug data . Donepezil users were matched with patients from the same site who were not receiving donepezil on the basis of dementia severity (AD, non-AD dementia, or dementia with etiology unspecified). *Assessments:* up to 2 years.	n= 10864 (donepezil users plus matched non-users) 1. nursing home residents with dementia receiving donepezil 5 or 10mg/day (n=5423) 2. matched non-users of donepezil (n=5423). *Age range:* at least 65 years (mean 83)	*Primary Outcome* Mortality

Abbreviations: AD: Alzheimer's Disease; **DB**: double-blind; **RCT**: randomised controlled trial. **ADAS-cog:** Alzheimer's' Disease Assessment Scale Cognitive Sub-scale; **BPSD:** Behavioural and Psychological Symptoms of Dementia; **CDR-SB**: Clinical Dementia Rating – Sum of the Boxes; **CGI:** Clinical Global Impression; **HDS-R:** Hasegawa Dementia Scale; **IDDD:** Interview for Deterioration of Daily Living Activities in Dementia; **IndiSS:** Individual Symptoms Score; **MMSE:** Mini Mental State Examination; **QoLS:** Quality of Life Scale.

The relevant findings from each of these observational studies are presented below in Table 8. The research question addressed by each study is noted, together with a commentary on how well the findings address each question.

Table 8. Summary of Results of New Observational Studies Relevant to Clinically Important Research Questions

Study/refs	Design	Participants	Research Question	Results Pertinent to Research Question
Efficacy and safety of donepezil over 3 years, an open label, multicentre study in patients with mild to moderate AD (Burns 2007)	***Design:*** Prosepctive, Open-label extension. *Phase 1*: A 24-week DB, placebo controlled RCT (donepezil 5-10mg, or placebo). *Washout phase:* **treatment discontinuation:** 6-week single blind placebo washout **Phase 2: 132-week Open-Label extension. Donepezil 5 or 10mg.**	***Numbers:*** 579 patients	**Is there any evidence of harm resulting from discontinuation of ACHEI at any stage of illness?** Yes, as the significant, dose-related cognitive benefits and improvements in global function that were gained during 24 weeks of double-blind treatment with donepezil were lost during the 6-week placebo washout period, prior to the start of open-label treatment.	**Cognition (ADAS-cog):** *Phase 1: DB Phase:* + (donepezil vs. placebo) *Washout phase:* **Cognitive improvements lost** *Phase 2: Open –Label extension:* Improved up to 24 weeks. **Global (CDR-SB):** *Phase 1: DB Phase:* + (donepezil vs. placebo) *Washout phase:* **Global improvements lost** *Phase 2: Open –Label extension:* Improved up to 12 weeks.
Effects of donepezil on neuropsychiatric symptoms in patients with mild to moderate AD and behavioural and psychological symptoms (Tanaka 2008)	***Design:*** Prospective, Observational study. Patients showing at ≥ one BPSD of hallucinations/delusions, wandering, and aggression. **12-weeks Observational:** patients receiving donepezil 3- 5mg.	***Numbers:*** *252 patients*	**Is there any real life evidence on caregiver burden for AChEIs as a class?** Yes, 54.1% of caregivers reporting that their burden had decreased at the end of the 12-week donepezil treatment period, mirroring the improvement in behavioural symptoms.	**Caregiver's burden:** (Patients who posed 'no burden' to their caregivers before and after treatment were excluded from analysis.) **Caregiver 'burden decreased' in 54.1% of caregivers; and 3.6% patients posed 'no burden' to caregivers at study end.**
Donepezil in patients with mild to moderate AD: a clinical observational study evaluating individual symptom scores (Riepe 2007)	***Design:*** Prospective, Observational study. **6-month Observational:** patients receiving donepezil 5 or 10 mg	***Numbers:*** 2004 patients	**Is there any benefit of continued use of AChEIs irrespective of severity in terms of prevention of increased use of anti-psychotics?**	**Anti-psychotic use:** A trend towards decreased use of anti-psychotic medication observed: 37% at baseline, 28% at 6 months. Reductions in use of neuroleptics, antidepressants, and sedatives/sleep medications.

Study/refs	Design	Participants	Research Question	Results Pertinent to Research Question
Effect of donepezil on mortality rates in nursing home placements with dementia (Gasper 2005)	***Design:*** Retrospective, matched cohort, Observational study. **2-year Observational**: nursing home residents with dementia, receiving donepezil 5 or 10 mg. Donepezil users matched with patients from the same site who were not receiving donepezil on the basis of dementia severity.	***Numbers:*** 10864 nursing home residents with dementia 1. patients receiving donepezil 5 or 10 mg (n=5423) 2. matched non-users of donepezil (n=5423)	**Is there any benefit of continued use of AChEIs irrespective of severity in terms of prevention of increased use of anti-psychotics?**	**Mortality** **+** : Patients receiving donepezil statistically significant lower mortality rate over 2 years vs. non-users, which remained after adjusting for concomitant use of antipsychotic drugs.

(+) statistical significance. **AD:** Alzheimer's Disease; **ADAS-cog:** Alzheimer's' Disease Assessment Scale Cognitive Sub-scale; **BPSD:** Behavioural and Psychological Symptoms of Dementia; **CDR-SB:** Clinical Dementia Rating – Sum of the Boxes; **DB:** Double blind; **RCT**: Randomised controlled trial.

2.4.1 Is there any evidence of harm resulting from discontinuation of AChEIs at any stage of illness?

The AWARE study (Johannsen et al., 2006, discussed in *Section 2.3.4* above and included in 2004 submission) provides support for not stopping AChEI treatment because there has been "no apparent clinical benefit." Rather they show that an observation period of six months is essential to determine optimum treatment benefits with donepezil, and that before that time treatment benefit may be difficult to perceive. Two meta-analyses described here (Wilkinson et al., 2009; Burns et al., 2008) confirm this view. In the Wilkinson analysis which evaluated clinical worsening, as defined by a decline in cognition, global ratings and function, among patients meeting the criteria for clinical worsening, patients who received placebo had greater cognitive decline than those who received donepezil. In the responder analysis of Burns (2008), patients defined as non-responders on the CIBIC-Plus still demonstrated a mean improvement from baseline in ADAS-cog score. These studies point to the difficulty in assessing treatment response. Many donepezil-treated patients characterised as 'non-responders' according to traditional markers of treatment success may still derive benefits. Therefore, treatment should not be discontinued on the basis of an apparent lack of response; the harm in doing so is that the patient never has an opportunity to benefit from the treatment.

The 24-week, double-blind placebo-controlled withdrawal study (Holmes et al., 2004) specifically enables an evaluation of the effects of drug withdrawal. All patients enrolled were first treated in an open-label phase with 5 mg/day donepezil for six weeks followed by 10 mg/day donepezil for a further six weeks. Patients were then randomised to receive placebo or donepezil 10 mg/day for six weeks followed by a further six weeks provided there was no marked cognitive deterioration. Following open-label treatment with donepezil, patients randomised to placebo showed a significant worsening of neuropsychiatric symptoms and a worsening of caregiver distress at both six and 12 weeks post-randomisation compared with a continued improvement in those who remained on donepezil treatment. In the case of this study, the harm resulting from discontinuation of AChEIs is the re-emergence of neuropsychiatric symptoms and an increase in caregiver stress. This study clearly points to the need for continued AChEI treatment.

The long-term, open-label RCT discussed above (Burns, 2007) demonstrates a further reason why treatment should not be discontinued. In this study, the significant, dose-related cognitive benefits (ADAS-cog) and improvements in global function (CDR-SB) that were gained during 24 weeks of double-blind treatment with donepezil were lost during the six-week placebo washout period, prior to the start of open-label treatment. At the end of the double-blind treatment phase (Week 24), the mean ADAS-cog score of patients randomised to receive donepezil 10 mg/day was still better than at baseline. However, after the six week washout period, the mean ADAS-cog score of all patients was approximately 3 points worse than it had been at baseline of the double-blind phase of the study. On starting open-label treatment, mean changes in ADAS-cog scores of all patients was improved by approximately 2 points after six weeks, and 1 point after 12 weeks, compared with the start of open-label treatment. It has previously been suggested that the benefits of treatment, lost on stopping, may not be fully regained when donepezil is reinitiated (Doody et al., 2001). Indeed, in this study, when

donepezil treatment is re-initiated in the open-label phase, cognition and global function improve, but not to pre-washout levels.

These findings have important implications for the treating physician and suggest that, once initiated, donepezil treatment should be continued. It should not be stopped arbitrarily, or solely on the basis of MMSE score cut-points (1) because treatment benefit may not yet have been achieved, and (2) because to do so will undo whatever treatment benefit has been attained (which may go unrecognized until treatment is stopped). Where donepezil treatment has been continued for an adequate period of time, adding memantine on top of donepezil treatment is an effective treatment strategy (see Section 2.3.3.4 above) preferable to stopping donepezil altogether.

2.4.2 Is there any real life evidence on caregiver burden for AChEIs as a class?

We have already discussed two RCTs (Section 2.3.3.2.5; Feldman et al., 2001, 2003; Holmes et al., 2004) in which improvement in neuropsychiatric symptoms with donepezil is accompanied by a reduction in levels of caregiver stress. These results are supported by those of a 12-week, open-label, multicentre, obervational study, in 252 patients with mild to moderate AD showing at least one of the 'behavioural and psychological symptoms of dementia' (BPSD) of hallucinations/delusions (64% of patients), wandering (36.1% of patients) and aggression (49% of patients; Tanaka, 2008) demonstrated that donepezil has a positive effect on the behavioural symptoms of AD, including mood disturbances, delusions, wandering and aggression. It has been noted (Chapter 1) that the behavioural symptoms of AD are the most troubling to the caregiver. Indeed, the improvement in behavioural symptoms that was observed in Tanaka 2008 with 12 weeks of donepezil treatment was mirrored by an improvement in caregiver burden, with 54.1% of caregivers overall reporting that their burden had decreased at the end of the 12-week treatment period. Moreover, the proportion of caregivers who reported no burden or a decreased burden at Week 12 was even higher for patients in whom BPSD symptom relief was observed, and ranged from 88.5% to 94.4% of caregivers of patients in whom relief of the BPSD symptoms of wandering and hallucinations/delusions were relieved, respectively.

2.4.3 Is there any benefit of continued use of AChEIs irrespective of severity in terms of prevention of increased use of anti-psychotics?

The issues surrounding the use of anti-psychotic medication have been discussed at some length in Chapter 1. One six-month, multicentre, prospective, observational study in 2046 patients with mild to moderately severe AD identified in the current literature search (Riepe et al., 2007) supports previous studies, showing a trend for less use of anti-psychotic medication during donepezil treatment. At baseline, 37% of the 747 patients were receiving psychotropic agents. This had dropped to 33% after three months of donepezil treatment and to 28% after six months of treatment. Specifically, reductions were seen in the use of neuroleptics, antidepressants and sedatives/sleep medications which were used by 16%, 11%, and 7% of patients, respectively, after six months of donepezil treatment. A reduction in the use of anti-psychotic medication use has significant implications for patient morbidity

and mortality and by improving patient outcomes, is expected to result in overall reductions in the total cost of AD. It is, moreover, in accordance with the goals of the *National Dementia Strategy.*

2.5 Safety

With over 5.6 billion days of patient treatment, donepezil has been demonstrated to be well tolerated. As for the AChEIs as a class, most adverse events associated with donepezil use are related to the cholinergic system and generally affect the gastrointestinal and nervous systems. For the majority of patients, adverse events are mild and transient, resolving without dosage alteration. In a recent meta-analysis of 22 placebo-controlled RCTs of donepezil, rivastigmine and galantamine (Hansen et al., 2008), the most frequently reported AEs were nausea (19% of subjects); vomiting (13%); diarrhoea (11%); dizziness (10%) and weight loss (9%). In this analysis the mean frequency of these events was lowest for donepezil and highest for rivastigmine.

The safety results of the new RCTs and prospective longitudinal studies identified in the systematic review for this submission, and which report sufficient safety data are summarised in Table 9. These data are consistent with those reported previously and do not alter the tolerability profile of donepezil. The safety results of Bullock 2007 confirm earlier reports that the frequency of AEs is highest during the dose titration phase with some resolution during the dose maintenance phase. Nonetheless, in this study, there were significant differences, in favour of donepezil in the incidence of several AEs as well as significant differences in withdrawals between donepezil and rivastigmine in favour of donepezil after two years of treatment (182/499 vs 234/495; odds ratio, 0.64; 95% CI 0.50 to 0.83; p=0.0006; Birks et al., 2006). Rivastigmine was also associated with a higher incidence overall of gastrointestinal AEs (Bullock et al, 2005).

Likewise, Burns (2007) reports that analysis of the first occurrences of individual AEs experienced by at least 10% of patients reveals that most AEs took place during the first 24 weeks of open-label treatment and that there was no marked rise in the incidence of these AEs with continued therapy. Over the three years of that study, the AEs most often leading to discontinuation were agitation (2%), confusion, death, depression, deterioration in the patient's condition and nausea (each 1%).

As noted in the summary of the product characteristics for donepezil, AChEIs may have vagotonic effects on heart rate (e.g., bradycardia). AChEIs can provoke syncope, a symptom that involves brief loss of consciousness with spontaneous recovery and is usually accompanied by falling (Kapoor, 2000). One population-based cohort study, in 19,803 community-dwelling older adults with dementia who were prescribed AChEIs and 61,499 controls who were not, found that hospital visits for syncope were more frequent in people receiving AChEIs than in controls. Use of AChEIs has been associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia (Gill et al., 2009). However, syncope has not been identified as an AE in the RCTs and prospective longitudinal studies reported here (Table 9). In addition, Burns (2007) reports that no cases of bradycardia that were considered to be serious AEs were associated with serious AEs of syncope.

Table 9. Summary of Safety Data from RCTs, Direct Comparator Study and one Open-Label Study

Study	Study Duration	Treatment (n)	Any AE n (%)	Serious AE n (%)	Discontinuation due to AE n (%)	Specific AE† n (%)						
						Nausea	Weight decreased	Diarrhoea	Seizure	Agitation	Fall	UTI
AD2000 Study: Long-term donepezil in mild to moderate AD (Courtney 2004)	3 years	**Donepezil** (242)		29 (12.0)	36 (14.9)							
		Placebo (244)		23 (9.4)	20 (8.2)							
Long-term (2 year) donepezil or rivastigmine in moderate to severe AD (Bullock 2005) Week 1-16: Titration phase Week 17-104: maintenance phase	Titration phase: 16 weeks	**Donepezil** (499)	323 (64.7)	162 (32.5) 157 (31.7) (denotes data for whole study period)	35 (7.0)	76 (15.2)	9 (1.8)	34 (6.8)		50 (10.0)	10 (2.0)	13 (2.6)
		Rivastigmine (495)	403 (82.0)		70 (14.1)	163 (32.9)	30 (5.1)	41 (8.3)		35 (7.1)	25 (5.1)	8 (1.6)
	Maintenance phase: 20 months	**Donepezil** (453)	349 (76.9)		64 (14.1)	24 (5.3)	43 (9.5)	30 (6.6)		47 (10.4)	44 (9.7)	26 (5.7)
		Rivastigmine (404)	318 (78.7)		42 (17.9)	52 (12.9)	36 (8.9)	26 (6.4)		34 (8.4)	33 (8.2)	18 (4.5)
Efficacy and safety of donepezil over 3 years, an open label, multicentre study in patients with AD (Burns 2007)	3 years	**Donepezil** (579)	492 (85)		87(15)	64 (11)		69 (12)			58 (10)(**a**)	

(**a**): accidental fall; **UTI**: Urinary tract infection.

†The AEs shown are those that occurred with a frequency of 5% or more in the donepezil treatment arm during maintenance therapy in the Bullock study.

2.6 Discussion

AChEIs are now the standard of care for dementia in most Western countries. Their use in the UK over the last several years has increased, though not to the same extent as seen in other major Western countries. In the opinion of Eisai and Pfizer, the pharmacological management of AD is still inadequate in the UK with patients not receiving AChEI treatment early enough in the course of the disease for them to achieve the maximum therapeutic benefit. This is inconsistent with the aims of the *National Dementia Strategy*. Current NICE guidance recommends the use of AChEIs in patients with moderate AD only (defined as an MMSE score of 10-20). This submission provides additional clinical evidence on the effectiveness of donepezil in the symptomatic management of AD from the mild through to the moderately severe disease stages based on a systematic literature search. The new studies have been presented in the context of the clinical evidence from the 2001 and 2004 submissions and indicate that donepezil should be available for AD patients in the mild stages of the disease.

2.6.1 Effects of Donepezil on Cognition and Function

The RCT evidence base for donepezil (as identified by the literature search protocols employed for the 2001, 2004 and current submissions, and consisting of 12 placebo-controlled RCTs in total (Table 3) demonstrate the benefits of donepezil on cognition in patients with mild to moderate AD.

Four of seven RCTs in which ability to perform ADLS was measured also demonstrated a positive effect in favour of donepezil on at least one scale and a recently published meta-analysis of seven donepezil RCTs found a statistically significant advantage favouring donepezil versus placebo on the function domain (Hansen, 2008). The implications of maintaining functional abilities are far-reaching in that ADL competency can logically be related to quality of life for both the patient and carer. Furthermore, there is undoubtedly a correlation between stabilisation of ADL abilities and the likelihood of remaining independently resident in the community rather than within a nursing home setting. Three meta-analyses (Wilkinson et al., 2009; Burns et al., 2008; Hansen et al., 2008) of individual RCT studies further confirm that donepezil produces benefits in cognition and function in mild to moderate AD.

Although RCTs are the gold standard of study design, observational studies have a number of important advantages. They increase the generalisability of the results; better reflect real life clinical practice situations; and can be conducted over longer periods. Thus, the information they provide complements that from RCTs. Two prospective longitudinal studies (Burns et al., 2007; Wallin et al., 2007) included in the evidence presented here show that donepezil is effective for up to three years in real-world settings. In the study by Wallin (2007), 50% of patients treated with donepezil were considered unchanged or improved on their global assessment after one year.

This is a significant treatment benefit with huge implications for patient and caregiver. Not only was donepezil shown to be effective in the long term, but Burns et al. (2007) suggested that there was no attrition of treatment benefit over three years. This means that the treatment benefit attained on initiating donepezil treatment, in terms of improved cognition and function, is maintained for as long as treatment continues relative to the declines observed in untreated cohorts of AD patients.

2.6.1.1 Evidence for the Use of Donepezil in Mild AD

Donepezil is the only AChEI for which an RCT has been conducted in an exclusively mild patient cohort (MMSE 21-26; Seltzer et al., 2004). In this 24-week placebo-controlled RCT, the treatment difference between donepezil and placebo at end point was 2.3 (p=0.001) points (LOCF) on the ADAS-cog and 1.8 (p=0.002) points on the MMSE. The results of the meta-analysis of individual patient data on cognitive function (Murthy 2008) which demonstrates that donepezil produces statistically significant improvements in cognition relative to placebo in patients with mild AD, are in accordance with the RCT findings of Seltzer (2004). A second meta-analysis (Prodafikas 2009) showed that donepezil produced statistically significant benefits in the global function of patients with mild AD. Moreover, the observed treatment effects for function were greater in the mild compared with the moderate cohort, suggesting that earlier treatment may be associated with greatest treatment benefit. Likewise, in a meta-analysis by Wilkinson (2009) the percentage of donepezil-treated patients showing clinical worsening was greater in patients with moderate compared with mild AD.

Taken together, this constitutes more evidence in mild patients than for any other AChEI and presents a compelling argument for initiating donepezil treatment in the mild stages of the disease. If patients can initiate treatment while at a higher cognitive and/or functional level (that is, in the early stages of the disease) they will gain greater treatment benefit than they would if they waited until their cognition and/or functional levels had deteriorated (in the moderate stages of the disease). In addition, their progress to more advanced stages of the disease is delayed. In another RCT included in the 2004 submission, greater levels of preservation of cognition, global function and ADLs were seen for patients receiving early and continuous treatment with donepezil compared to those whose treatment was delayed by one-year (Winblad 2006).

2.6.2 Effects of Donepezil on Behaviour and Measures of Caregiver Burden

As discussed in Chapter 1, caregiver burden is most associated with the neuropsychiatric symptoms of AD, but most caregiving time is spent assisting patients with ADLs. Caregiver time devoted to helping the AD patient typically increases with the severity of the disease and is associated with significant costs as carers are unable to work, and experience deteriorating health. In the first analysis of caregivers actively providing care at study baseline within a clinical

study of AChEI treatment, Wimo and co-workers (2004) (in a sub-analysis of the Nordic study (Winblad et al., 2001)) showed that treatment with donepezil has significant implications for the caregiver: by 12 weeks, the caregivers of donepezil-treated AD patients were providing less care than at the baseline of the study. Moreover, for nine months, the time burden of care for the donepezil-treated patients remained less than at baseline. At the one-year timepoint carers of donepezil-treated patients were spending approximately one hour less per day caring than the carers of patients who had received placebo. The primary outcome measure in this study was the Resource Utilization in Dementia, a measure of time spent caring, as opposed to the stress or burden that caregiver's experience.

Of five RCTs (Table 3) reporting on caregiver outcomes, three reported positive benefits for donepezil relative to placebo. In two of these studies the caregiver outcomes were measures of caregiver stress (as opposed to caregiver time as reported in Wimo et al 2004 above) and in both, the positive benefits of donepezil compared with placebo on levels of caregiver stress were mirrored by its positive effects on the neuropsychiatric symptoms of the disease. The meta-analysis by Campbell et al. (2008) (which includes a pooled analysis of six donepezil RCTs) provides strong confirmation that donepezil has a positive effect on the neuropsychiatric symptoms of AD.

Increasingly, there is an understanding that the symptomatic benefits of AChEIs may translate into delayed entry to nursing home care. As patients become increasingly incapacitated due to loss of more basic functions (e.g. dressing, bathing, toileting), caregivers often experience considerable strain from increased demands on their time, physical burdens of care, stress of managing patients' troublesome behaviours, and changes in work status as a result of caregiving. Nevertheless, delaying nursing home placement was rated by 77.5% of AD caregivers in one study as "extremely important" or "very important" (Karlawish 2000) and remaining at home longer is a goal for both patients and caregivers (Mittelman 1996). Although we have no RCT evidence to indicate an effect of donepezil in delaying institutionalisation, an observational study presented in the 2004 submission showed that sustained use of an effective dose of donepezil in the early or intermediate stages of AD for at least nine months was associated with a significant delay in temporary and permanent nursing home placement of almost 2 years (Geldmacher 2003). Moreover, these results reinforce the importance of sustained use of donepezil in treating AD.

2.6.3 Maintenance of Donepezil Treatment

The evidence for donepezil demonstrates that there is significant potential for harm from discontinuing therapy. One issue is that the treatment benefits attained while on treatment are rapidly lost on stopping (Burns et al., 2007). Treatment benefit may not be obvious until treatment

is stopped, but once lost these benefits may not be fully regained when donepezil is reinitiated (Doody et al., 2001). The treatment benefits lost on stopping treatment in the study by Burns et al (2007) were in the domains of cognition and function. Behaviour, too, has been shown to deteriorate on stopping treatment (Holmes et al., 2004) with a concomitant increase in caregiver burden. As caregiver burden is a significant predictor of institutionalisation, it seems reasonable to assume that worsening behavioural symptoms, produced by stopping treatment, may hasten nursing home placement.

Thus, a perception that there is no treatment benefit, resulting in cessation of treatment, puts the patients at great risk. Johanssen et al. (2007) demonstrated that an observation period of at least 6 months may be required before any treatment benefit can be ascertained. However, it is also important to be aware that repeated multi-domain assessments are essential in the evaluation of treatment benefit. The meta-analyses by Wilkinson and co-workers (2009) and by Burns and coworkers (2008) demonstrate that lack of response in one domain does not mean that there is no treatment benefit. Thus, an initial decline or stabilisation in MMSE score is not necessarily indicative of a lack of treatment effect. Moreover, treatment 'response' in a progressive neurodegenerative disease can encompass a variety of outcomes, including short-term improvement, long-term stabilization or a less than expected decline in one or more clinically relevant symptoms or symptom domains.

Rather than stopping donepezil treatment, the evidence demonstrates that adding memantine is a reasonable treatment strategy (Tariot et al., 2004). Donepezil and memantine have differing mechanisms of action and preclinical studies show that memantine does not affect the inhibition of AChE by donepezil, nor does it bind to muscarinic receptors (Wenk et al., 2000; Parsons et al., 1999; Danysz et al., 1997). In addition, no pharmacokinetic or pharmacodynamic interactions between memantine and donepezil have been observed (Periclou et al., 2003). It has been demonstrated that the discontinuation of donepezil treatment is detrimental to the patient; therefore, any potential benefits of memantine might be negated by the detrimental effects of withdrawing donepezil. Thus, adding memantine to treatment with donepezil is the safest option for patients.

2.6.4 The Effect of Donepezil on Anti-psychotic Use

As anti-psychotic medications are used to moderate behavioural symptoms in AD patients, it seems reasonable to assume that whenever behavioural disturbances worsen, anti-psychotic use will increase, if symptoms are not being managed effectively using an AChEI. We have identified one observational study demonstrating that donepezil use is associated with a reduction in the use of neuroleptics, antidepressants, and sedatives/sleep medications (Riepe et al., 2007). This supports other studies not included in the evidence presented here that have shown that patients

who had never been exposed to AChEIs use more antipsychotic drugs than those who used AChEIs (Lopez et al., 2002). In addition, the use of antipsychotic drugs has been associated with increased risk of functional and cognitive decline and admission to a nursing home (Lopez et al., 1999; McShane et al., 1997) and the use of sedative/hypnotic drugs has been associated with death (Lopez et al., 1999). Furthermore, in a retrospective cohort study in patients receiving donepezil or galantamine, use of anti-psychotics was significantly associated with risk of mortality (Lopez-Pousa et al., 2006). Thus, anti-psychotic drug use is highly detrimental to the AD patient and minimising their use in this patient population through effective, sustained use of donepezil is in accordance with one of the aims of the *National Dementia Strategy*.

2.7 Conclusions

The new evidence included in this dossier supports and extends the clinical evidence presented in the two earlier submissions to NICE for the demonstrable benefits of treatment with donepezil in both mild and moderate AD. These benefits are realised in multiple domains including cognition, global function, ADL function, behaviour and quality of life and are sustained over the long term. With improved cognition, function and behaviour comes a concomitant reduction in the time spent by caregivers in caring and a reduction in the burden they experience.

In particular, the efficacy of donepezil in patients with mild AD has been demonstrated. Treatment benefit conferred by donepezil may be larger in the mild compared with the moderate stages of the disease. Moreover, treating patients in the early stages of AD enables them to stay in the early stages for longer, delaying their progression to more advanced stages, where symptoms are more severe. Treating the symptoms of AD across the AD spectrum from its earliest stages has enormous implications for the well being of patient and caregiver, with attendant consequences for society. We suggest that a broadening of the NICE recommendations to include patients with mild disease will provide the impetus for early diagnosis in accordance with the goals of the *National Dementia Strategy.*

The evidence also points to the need for early and continued implementation of donepezil therapy. It demonstrates that it is very difficult clinically to determine the treatment effect of an AChEI in a particular patient; thus, even in patients where no therapeutic benefit was deemed to have occurred, RCT evidence demonstrated benefit from continued use of donepezil (Johannsen et al., 2006). Moreover, the evidence has shown that treatment benefit can be attained across multiple domains that include cognition, function, behaviour, caregiver burden and delay in admission to nursing homes. In light of this, it is illogical and potentially harmful to individual patients to recommend stopping donepezil treatment based solely on crude MMSE criteria. Rather this is a sensitive clinical decision for a specialist to make based on an understanding of the individual patient.

SECTION 3 – COST-EFFECTIVENESS OF DONEPEZIL

3.1 Executive Summary

- A literature search designed to identify economic studies published since 2004, found four cost effectiveness studies relevant for the UK. These studies had the following limitations:
    - The efficacy of the AD treatments is often represented by a single scale, usually cognition (e.g. MMSE) which does not capture the full nature of the disease and treatment benefits.
    - Aggregated health states were used which were not able to capture treatment benefits in adequate sufficient detail.
    - Cohort model approaches used did not consider individual characteristics in predicting outcomes, variability in outcomes over the course of the disease or other factors that impact long term outcomes, such as persistence with treatment.
    - They were based on short term (6 months or less) clinical trial evidence.
- A de novo economic model was developed for this submission which uses discrete event simulation to provide a more detailed and accurate estimate of the cost effectiveness of donepezil. This approach is able to capture the individual variability between patients in terms of disease progression, treatment success and mortality. In particular, the model has the following advantages:
- Continuous measurement of health and disease progression on multiple scales (MMSE, NPI, ADL, IADL);
- Multivariate predictors of patient and caregiver utilities based on continuous measures of disease severity and finer gradations of severity in the assignment of costs and nursing home care;
- Incorporates estimates of donepezil efficacy based on multiple long term (up to 12 months) follow up randomised controlled trials;
- Base case analyses based on current list price show that donepezil is cheaper and more effective (dominates) compared with no treatment in both mild and moderate AD patients in the UK in the base case analyses.
- Both QALY gains (mild 0.133 vs. moderate 0.098) and total cost savings (£3,300 vs £1,900) estimated for donepezil are greater in the mild patient group as compared to the moderate patient group.
- In both mild and moderate AD patients, the acquisition cost of donepezil can be offset by reductions in the need for social services, physician visits and institutionalisation that are already evident during the first 1-2 years of treatment.

- Extensive one way sensitivity analyses show that donepezil remains cost effective in both the mild and moderate patient subgroups under almost all plausible changes in model parameters. Donepezil becomes more cost effective than in the base case, if acquisition costs are assumed to fall following the entry of generics post loss of patent exclusivity in 2012.
- Other one-way sensitivity analyses show that donepezil becomes more expensive and more effective only when there are very large reductions in nursing home costs or reductions in overall costs of care specifically for the patients who move into the severe stages of AD. Even in these analyses the cost per Quality Adjusted Life Years (QALYs) are well below the £20,000 threshold (£1,370/QALY and £7,093/QALY respectively) in the moderate AD population. Among patients with AD of mild severity, reducing nursing home costs by 50% resulted in an ICER of £1,866/QALY.
- Probabilistic analyses demonstrate that the probability that the cost effectiveness estimates for donepezil remain below the £20,000 threshold are 74% for the mild AD population and 70% for the moderate population.

3.2 Summary of the Health Economic Section of the Previous Submission

In the 2004 donepezil submission, the economic analysis found an incremental cost-effectiveness ratio for donepezil in combination with usual care as compared to usual care alone of £1,206 per year of non-severe AD gained. Probabilistic sensitivity analyses indicated that the probability that donepezil would dominate no pharmacologic treatment was 37%.

The treatment of patients with an initial MMSE score of 10 or higher with donepezil combined with usual care versus usual care alone was found to be cost-effective. Results were found to be sensitive to variations in the mortality rate, and assumptions regarding the length of drug benefit. The highest ICER (£23,162 per year of non-severe AD) resulted from assuming that all drug benefits disappear at one year.

3.3 Overview of Economic Studies Published Since the Previous NICE Guidance

A number of economic studies have been published on AD since the previous NICE guidance in 2004 (see Appendix G for list of all studies identified in a targeted electronic search). These include UK specific economic evaluations (Green 2005, Loveman 2006, Gustavsson 2009, Getsios 2010) and a cost of illness study (Luengo-Fernandez 2010) which are summarized below. In addition, four reviews have been identified that discuss health economic modelling in AD in general (Cohen 2008, Green 2007, Oremus 2008, Bosanquet 2006). The UK specific studies and review papers are summarized below.

As highlighted in the Background section, a very recent UK report estimated the cost of dementia in the UK to be £23 billion per year (Luengo-Fernandez et al., 2010) including social care costs (long-term nursing and residential care); health care costs (primary care, accident and emergency visits, outpatient and inpatient care, medication and private care); and indirect costs (or informal costs including hours of unpaid care provided by carers, working years lost (mortality) and incapacity days (morbidity)).

Long-term institution care costs are estimated to be in excess of £9 billion per year, health care costs are £1.2 billion and 1.5 billion hours of unpaid care were provided by caregivers. With an estimated a monetary value of £12.4 billion, the costs associated with unpaid care constitutes the single largest component of the total cost of AD. Drug costs constitute less than 1.3% of total costs (Luengo-Fernandez et al., 2010).

The cost-utility model developed by the Southampton Health Technology Assessment Centre (SHTAC) as part of the NICE Technology Assessment TA 111 in 2004-2006 was published in different papers and has gone through a number of alterations. Originally, based on this model Green (2005) concluded AChEIs may not to be a cost-effective use of NHS resources with an incremental cost per QALY gained ranging from £53,780 to £74,735 over a five year time horizon (Green 2005). The same model published as the Health Technology Assessment Report (Loveman 2006), reached a similar conclusion and reported an ICER in excess of £57,000/QALY, £68,000 and £80,000/QALY for rivastigmine, galantamine and donepezil respectively, among patients with mild to moderately severe AD.

A number of concerns were raised about the model, inputs and assumptions and subsequently it went through a series of alterations. The final augmented base case prepared in 2009, included a number of important changes, including, incorporating utility benefit for carers, allowing for an effect of AChE inhibitors on behavioural symptoms, using alternative cost estimates, reporting results separately for mild and moderate AD patients, and correcting several technical errors. In the Final Appraisal Determination in 2009, the cost-effectiveness estimates for moderate AD patients ranged from £23,000 to £35,000 depending on the choice of AChE inhibitor and whether caregiver benefits were included. The cost-effectiveness estimates for mild AD patients ranged from £56,000 and £72,000 depending on the choice of AChE inhibitor and the inclusion of caregiver benefits. The most recent NICE Guidance, which recommended prescription of AChEIs for people with moderate AD, but not mild AD, are based on these final estimates (NHS England and Wales 2010).

The main objective of a cost utility study by Gustavsson et al (2009) conducted for the UK was to compare the use of AChEIs in patients with dementia with Lewy bodies to AD using three different models (the Southampton Health Technology Assessment Centre (SHTAC) model, and

a micro-simulation and a Markov model) both developed by the authors. As part of their analyses they showed that AChEIs in the treatment of AD have an incremental cost-effectiveness ratio (cost per QALY) in the analysis for “all AD cases” (baseline MMSE 20.3) of £67,904 in the micro-simulation model, of £194,066 in the SHTAC model, and of £123,935 in the Markov model. In the analysis for “moderate cases” (baseline MMSE 16.5) ICERS were £39,664 in the SHTAC model while cost-saving were found with the micro-simulation model. The analyses showed an influence of the model type on results, and indicate that the use of AChEIs in moderate AD may be cost saving (Gustavsson 2009). While the authors provide little detail on their methodology, the main limitation appears to be the timeframe for the efficacy data and the data sources used to establish effectiveness. Four months of data were used to model treatment effect and such a short timeframe is unlikely to adequately capture the benefits of extended treatment, especially in patients with mild disease. Furthermore treatment effectiveness was based on an open study with no control group, forcing the assumption that untreated patients would not experience any decline in cognitive function over the first four months. Outcomes and predictions were also based on MMSE alone, and did not consider function or behavioural symptoms.

Modeling techniques for AD have been subject to substantial debate in recent years. Existing health economic models have been evaluated and their strengths and weaknesses assessed. Cohen and Neumann (2008) identified a number of limitations such as a focus on cognition for the description of disease progression; the capturing of disease progression in health states which cannot adequately represent the multitude of factors that impact on outcomes; or the focus on solely drug treatment instead of a combination of therapeutic measures. The authors argue that models in AD should better present important aspects of AD and its progression (Cohen 2008).

Based on a systematic review of published pharmacoeconomic studies in AD Oremus (2008) concluded that results varied widely because of different models and assumptions used. Recommendations for further research in the area of AD modelling include improved data inputs, such as resource use collected in RCTs or prospective cohort studies, microcosting, as well as the use of more clinically relevant outcomes (Oremus 2008).

Green (2007) conducted a review of published economic models in AD and raised concerns regarding the model structure, especially in terms of reliance on cognition alone for the modeling of disease progression and effects on costs and outcomes. Further issues discussed concern data inputs as well as the treatment of uncertainty (Green 2007).

Bosanquet (2006) highlighted methodological shortcomings with the previously developed Southampton Technology Assessment Centre model. The binary outcome measure of delaying entry to full time care (FTC) was found to fall short of capturing the complete range of benefits of

AChEI treatment. Treatment benefit should not only be expressed in terms of cognition, but also include functional and behavioural aspects which the author sees as important drivers of nursing home placement (Bosanquet 2006).

In summary, these models published and reviewed prior to 2009 relied on aggregated health states, and therefore were not able to capture benefits in adequate detail. They have also generally defined disease either on single domains (e.g., MMSE) again, losing the ability to capture the full nature of the disease and treatment benefits. Although for example the AHEAD model (Caro 2001) included both cognition and behaviour to predict FTC, behaviour was measured crudely as the presence of hallucinations or delusions. In addition, most of these models were designed as cohort models with no ability to consider individual characteristics in predicting outcomes, variability in outcomes over the course of the disease or other relevant factors that might influence important determinants of long term outcomes, such as persistence with treatment.

To address some of the methodological issues identified by reviewers, a discrete event simulation (DES) model was developed by Getsios et al. and serves as the basis of the economic evaluation in the current submission (Getsios 2010). The authors estimate the cost effectiveness of donepezil treatment of patients with mild and moderate AD versus no treatment in the UK. The model used for the publication was updated with respect to costs. Methods and results are described in Section 3.3 below and in Appendix H.

3.4 Cost-effectiveness Model for Donepezil

This section summarizes the methods and results of a new cost-effectiveness model, which is different from the one used in the previous submission. A summary of the methodology and results are included here. Full details can be found in the technical report under technical report and the manuscript in Appendices H, I, J.

3.4.1 Rationale

The rationale for developing a new model is threefold. First, it is to address limitations of existing models that focus on a single measure of disease severity to model the evolution of AD alone. Second, it is to address structural limitations relating to a cohort models using Markovian structures. Third, it is to facilitate the inclusion of available longer term trial data, thereby reducing the period of extrapolations of treatment effect and capturing the benefits of treatment beyond 6 months.

An individual patient simulation is used that allows for consideration of variation in patient characteristics and disease progression, measures disease severity on multiple domains using

continuous measures of severity, and allows for simulation of persistence with treatment, implementation of clinical stopping rules, and time varying treatment effects.

The treatment goals of current AD therapy are to improve, maintain or at least slow the deterioration in cognition, behaviour and functional ability. A discrete event simulation model was designed to explore the health economic impact of donepezil in patients with AD in line with the multiple treatment goals. To achieve that, in the model disease severity and progression is measured based on cognition (using the MMSE), behaviour (using the Neuropsychiatric Inventory, NPI), activities of daily living (ADLs) and instrumental activities of daily living (IADLs). These measures represent the main characteristics of disease and compared to global scales, they allow for more precise estimates and differentiation in both disease progression and treatment effects. MMSE was selected based on its use in most of the donepezil trials (including pivotal clinical trials and because of availability of good quality long term follow up data for natural progression (CERAD) (Duke University 2009). NPI is the most commonly used scale for behavioral and psychological symptoms of dementia, with established links to health utilities in the literature. ADLs and IADLs are measured using information from a variety of scales. Selection criteria and methods for development of these generic ADL and IADL scales are provided in the technical report (Appendix H). Furthermore, the model was designed as an individual patient simulation. It considers individual characteristics in predicting clinical and patient reported outcomes via validated multivariate regression analyses (see Appendix I), thus providing a more precise assessment of benefits. With a more refined structure, the model can handle treatment discontinuation accurately and is able to show the impact of different treatment practices.

Key outputs besides costs and QALYs, now also include the time patients spend in less severe health states based on different scores (time spent with a MMSE score >10, with a NPI score <28, with ADL and IADL < 50, time spent in community and in institutional care). The main benefit of treatments such as donepezil is that patients are maintained in the milder health states for longer periods. An MMSE threshold of 10 for discontinuing treatment was selected in accordance with current NICE guidance. For NPI, a cluster analysis of psychiatric symptoms using the NPI of 122 Alzheimer's disease patients in the US (Tun 2007) was used as the basis for assigning a threshold of 28 for the NPI as representing highly symptomatic behavioural disturbances. IADL and ADL sores ranged from 0 to 100 and thresholds were arbitrarily set to their mid-point values of 50.

3.4.2 Patient Population in the Model

In accordance to specifications in the NICE scope for this appraisal, the economic model considers:

- patients with mild AD (MMSE between 20 and 26)
- and patients with moderate AD (MMSE between 10 and 19)

separately. An analysis considering both mild and moderate patients together was also conducted.

To make sure that model results reflect real life as much as possible, patients simulated in the model were created by sampling from an individual patient data set with baseline information on 826 patients from 3 donepezil clinical trials (Mohs et al. 2001, Winblad et al. 2001b, Feldman et al. 2001). The respective trials were chosen based on the availability and completeness of data on all characteristics required to populate the patient file used in the model. A trade-off had to be considered between the number of patients to include in the model and the completeness of input data available in the trials. Trials with more than one key clinical measure missing (e.g., ADLs, IADLs, and NPI) were not considered for inclusion to minimize the need for imputation, nor were trials conducted in special populations to ensure generalisability. The three trials that were included were judged to provide sufficiently large number of patients across all severity levels while involved only minimal imputation.

It is important to note that the choice of trials is unlikely to lead to bias since the information represents baseline data, i.e. both treated and untreated patients in the simulation are derived from the same baseline information.

Of note, while the patient file contains patients with severe AD, the model allows the user to specify the characteristics (including baseline MMSE scores) of patients to be simulated. For the current submission, patients with severe AD at baseline (i.e., MMSE <10) were not included in the analyses.

Characteristics recorded for each patient included patient age, sex, use of psychiatric medications, MMSE, NPI, ADL scores, and IADL scores, as well as caregiver age and sex. As mentioned, the trials chosen to provide the sample patients were those that had data on as many target variables as possible and taken together include all AD severity levels. Baseline data on NPI for one of the studies (Mohs et al. 2001) were not available and so were imputed based on a linear regression relationship to MMSE, age, and gender estimated from the other two trials. In order that the simulated population be representative of individuals with AD in the UK, the age and sex distributions of AD patients in the UK as reported in Dementia UK (Knapp et al. 2007) were used to assign sampling weights to the file. As a result, the overall age and gender distribution in the model is identical to the one reported in the Dementia UK report and is therefore representative of the UK making results more generalisable for the UK (see Figure 3 in the Technical Report, Appendix H). Data to derive sampling weights were not available by

severity strata, therefore there may be some deviation from characteristics of the UK population within severity strata.

Once patients are created in the simulation, an identical copy of each patient is created with the original patient assigned no treatment, and the copied patient assigned to treatment with donepezil 10 mg. By creating identical copies of each patient, the simulation ensures that the treatment comparisons are not being influenced by differences in patient characteristics.

For each treatment arm, an identical cohort of 1,000 patients is running through the model. Results are based on 20 replications of these 1,000 patients, so in effect, the model compares 20,000 patients treated with donepezil and 20,000 patients with no pharmacologic treatment. Note that although results are stable after 5 replications, they become very stable with only little deviation after 10 replications. To minimize unwanted variation, the final models were run with 20 replications.

3.4.3 Treatment and Comparator

In line with current NICE Guidance and the final scope for the Appraisal, the model compares donepezil 10mg per day to no pharmacologic treatment for patients starting treatment with mild disease.

In moderate disease the current NICE guidance recommends the use of cholinesterase inhibitors, however, consistent with the previous submission and in line with the majority of the clinical evidence, a comparison is made between donepezil 10mg per day and no pharmacological treatment. As stated in the Clinical effectiveness section it was not considered appropriate to compare donepezil with other cholinesterase inhibitors nor memantine, the variation in trial design across treatments may have a relatively large impact on any exercise trying to synthesize data, and is likely to make results of an indirect comparison of treatments uninformative and unreliable. In addition, all cholinesterase inhibitors (CI) are similarly clinically effective, as shown in systematic reviews (Birks 2006, Ritchie 2004, Hansen 2008, Raina 2008), and cost-effective versus no treatment, and that there is little differentiation between treatments in moderate AD patients. Although small differences exist in current treatment prices, this difference may be equalized by treatment costs related to titration. Furthermore, with loss of exclusivity for all AChEIs expected in 2012, current price differences will become less relevant in the near future. Therefore, it was felt that comparisons with other cholinesterase inhibitors would not be informative to decision-makers.

3.4.4 Time Horizon, Perspective, Discount Rate

The model adopts the perspective of the UK's National Health Service (NHS) and Personal Social Services to reflect the NICE reference case. The model was run over a time period of 25 years. Even though both the average survival of AD patients after diagnosis and the average treatment duration with donepezil observed in practice is much shorter, a time horizon of 25 years has been adopted to ensure that all possible effects are captured. Shorter time horizons are assessed in sensitivity analyses.

Both costs and effects are discounted at 3.5% per annum according to the NICE reference case specifications.

3.4.5 Model Framework and Structure

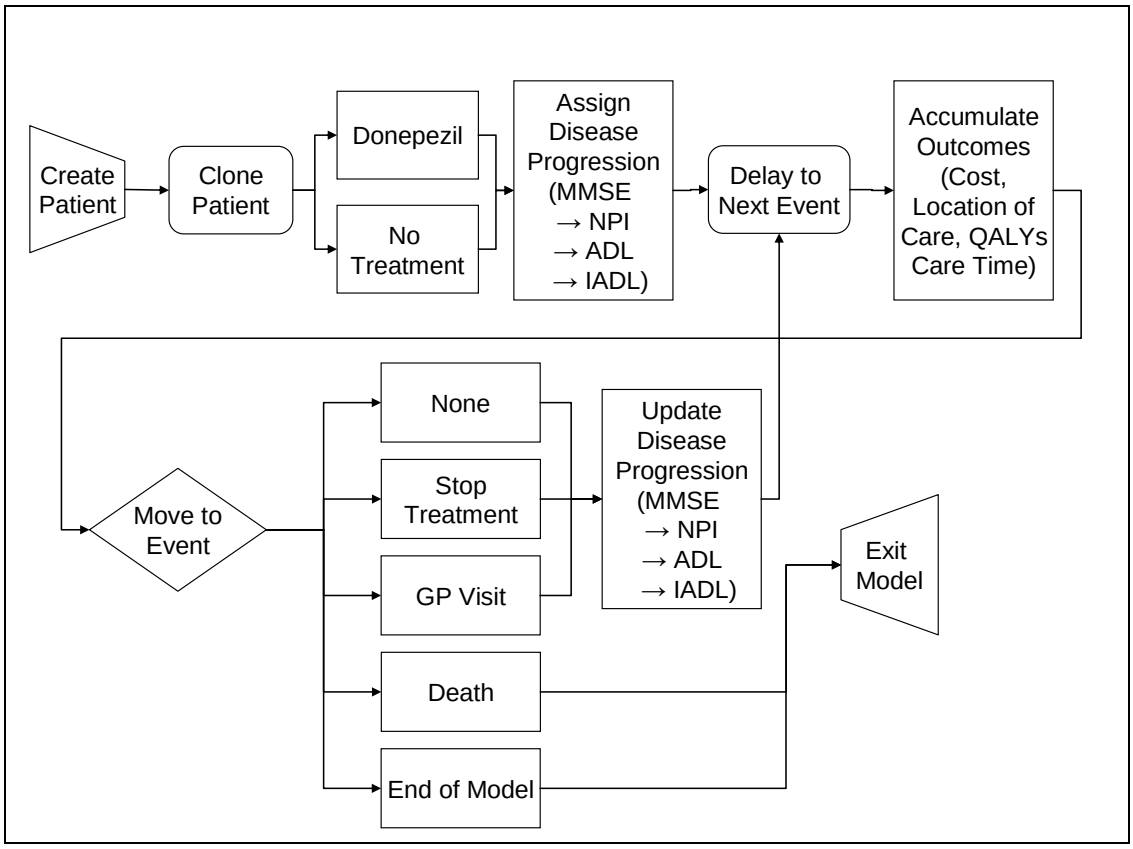
The model was constructed as a discrete event simulation. Discrete event simulation as a modeling technique allows individual patient level modeling, capturing heterogeneity in disease progression and other outcomes, as well as tracking correlated changes on multiple domains on continuous rather than discrete scales. The approach allows for a compact means of capturing the complexities associated with AD progression, and unlike a Markov modeling approach avoids the need to develop discrete health states. This is important for modeling outcomes in Alzheimer's disease, as it avoids the need to oversimplify the disease by, for example, restricting outcomes to requiring full time care or not requiring full time care, and thus masking the potential benefits of treatment, without necessitating a proliferation of intermediate health states which might make the model overly complex and development of transition matrices impractical. The discrete event simulation approach also allows for persistence with treatment to be captured in a realistic manner. By allowing individuals to be simulated, each with their own unique attributes which are updated throughout the simulation, discrete event simulation not only allows for more precise projections of patient experience, but is also computationally efficient, as it does not require continuous processing of patients – patients are updated only when events of relevance occur.

The simulation measures disease severity based on cognition (using the MMSE), behaviour (using the Neuropsychiatric Inventory, NPI), activities of daily living (ADLs) and instrumental activities of daily living (IADLs). Patients are followed over time with their disease characteristics and age updated at regular intervals capturing effect of treatment, disease progression and aging. Based on a given patient's treatment status and current disease severity, costs, health utilities and caregiver outcomes are calculated and accumulated over the appropriate time period. Consistent with current recommendations treated patients discontinue therapy once their MMSE scores fall below 10. Other treatment withdrawal is also incorporated into the model. Patient mortality is taken into account with mortality rates dependent on age and sex at baseline. No

strong evidence was found to support any treatment related improvement in survival, therefore mortality is modelled independently of treatment (see Section 3.4.8 below).

Figure 2 provides an overview over the model flow.

Figure 1. Simplified Representation of the Alzheimer's Disease Simulation Flow



3.4.6. Representation of Disease Progression and Treatment Effects in the Model

Disease progression was modeled not only based on cognitive decline, but also incorporating behavioural and functional abilities of patients. To adequately represent disease progression and treatment effects a set of regression equations were developed based on data from the CERAD (Consortium to Establish A Registry for Alzheimer's Disease) registry (CERAD) (Duke University Medical Center 2009), and seven donepezil clinical trials included in the Eisai/Pfizer repository spanning mild to severe Alzheimer's disease (Mohs 2001, Winblad 2001b, Feldman 2001, Rogers 1998a, Rogers Neurology 1998b, Black 2007, Winblad 2006a), including data from open label extensions of two of the studies (Doody 2001, Winblad 2006b). The inclusion of trials in the current analyses was based on a number of criteria. Patient level data had to be available, studies had to be in Phase III or later, and had to include baseline MMSE, and included at least one of the effectiveness outcomes of interest. Studies conducted in special populations (e.g.,

women only, Apo-E subtypes, NH only); or of open label design were excluded, along with dose finding studies.

CERAD data were used to assign the baseline rates of progression in MMSE, but the trial data provided a richer source of data on which to base predictive equations for changes in NPI, ADLs, and IADLs over time. Data on behavioural symptoms were only collected for a small subset of the CERAD population which would not have allowed for correlated measures of disease progression amongst the different scales of disease severity. In addition to allowing the different measures to be linked to each other by incorporating changes in one scale as predictors of changes in other scalesclinical trial data were the only source used to assign treatment effects for MMSE, NPI, ADLs, and IADLs.

Donepezil clinical trial data only were used to assign treatment effects for MMSE, NPI, ADLs, and IADLs. Data used from the trials included two open label extensions. One of these open label extensions was used to inform predictions on the natural progression of the disease only (Winblad 2006) and not to estimate treatment effects. The other open label extension was used to estimate the treatment effect on MMSE but based only on data for patients continuously treated with donepezil in this study excluding patients crossing over from the placebo arm of the study to the donepezil arm (Doody 2001). The inclusion of part of the open label study (i.e., data before 52 weeks) was considered acceptable because there were sufficient numbers of trial patients on placebo with similar characteristics over this period to allow for a fair comparison. All treatment effects were estimated using data from the placebo controlled parts of the 6 trials, two of which provided data for up to 52 weeks.

While MMSE data over time were available from trial data, the CERAD data offered a longer time course of data on MMSE progression. Furthermore, the patterns of change observed in CERAD were more in line with what has been previously reported on progression of AD, with progression slowest over the mildest and most severe stages of the disease (Stern 1994, Mendiondo 2000, Mohs 2000). The trial data showed a positive annual rate of change in MMSE (i.e., improvement) over some ranges of MMSE, even in untreated patients. Using the trial data to model the natural history of MMSE changes in an untreated population would not have been appropriate, as it would have led to predictions of improved cognition in a subgroup of untreated patients (See Technical Report and Manuscript for Additional Details Appendix H, I).

A piecewise linear regression model was fitted to adequately capture the relationship between rate of change of MMSE, defined as annual change in score since previous measurement, and previous MMSE in CERAD. A different slope is allowed in different intervals of the MMSE scale, which reflects a different rate of change at different stages of the disease. The MMSE equation derived from these data has the following form:

$$AnnnualRat\quad eofDecline\quad = 5.4663\ -0.4299\ PM_1 - 0.0042\ PM_2 + 0.1415\ PM_3 - 0.0791\ \Pr evRate + 0.0747\ Age + \delta_i$$

Note: PM represents patients' previous MMSE measurement, partitioned over the scale of MMSE. PM_1 – PM_3 are calculated as: PM_1 = min(PrevMMSE, 9), PM_2 = max(0, min(PrevMMSE-9, 9)), and PM_3 = max(0, min(PrevMMSE-18, 12)). PrevRate is the patients' last known rate of decline, and age represents patients' age at baseline. δ_i represents a random intercept parameter, which allows the pattern of decline to vary from one patient to another. The MMSE scale itself ranges from 0 to 30. See Appendix H for more detail.

It is important to note that this equation is used as the basis for modeling changes in MMSE for both treated and untreated patients. Since CERAD did not include treated patients, the treatment effect itself, was quantified based on the clinical trials. A similar model to that derived from the CERAD data was fitted to the trial data to quantify the treatment effect. That model included the same independent variables as the CERAD equation, but also included terms for treatment effects. Based on the observed patterns of rate of decline in treated and placebo groups, 20 weeks was identified as a changing point in effect. After careful consideration of the data available a piece-wise linear model was chosen to maximize goodness of fit, as there were insufficient data points where MMSE was measured to derive reliable equations using alternate functional forms.

Only the treatment effect terms from the trial-based equations are used in the model, with all other terms in the equation based on parameter estimates derived from the CERAD data. Thus the only difference in the prediction of changes in MMSE for patients on and off treatment are the application of these treatment effect terms. For example, if the CERAD equations predicted an annual rate of MMSE change of -3 points for an untreated patient, and the relative treatment effect term from the trial equations was 2, an untreated patient's MMSE score would decline by 3 points in one year, while their treated counterparts score would decline by only 1 point.

The final equation with the calculated relative treatment effect included is below:

$$AnnnualRat\quad eofDecline\quad = 5.4663\ -0.4299\ PM_1 - 0.0042\ PM_2 + 0.1415\ PM_3 - 0.0791\ \Pr evRate + 0.0747\ Age + 6.16 * T_1 + 2.47 * T_2 + \delta_i$$

Note: T1 represents weeks in the period of week 1 to week 20 for patients treated with donepezil and takes the value of zero for untreated, and T2 represents weeks between week 20 and 52 for patients on donepezil and takes the value of zero for untreated[1].

After week 52, continued treatment was assumed to have no further effect on the predicted rate of disease progression, and as with all treatment effects in the model, was assumed to serve to

[1] As described at the beginning of the section, only randomized controlled trial data is used to estimate effect for the 1st 20 weeks, while some open label data is incorporated in the treatment effect between week 20 and 52.

simply maintain previous gains. This is in line with previous AD model evaluations conducted on behalf of NICE which have assumed that treatment beyond the period where controlled clinical trial data are available only serves to maintain the initial benefit (Loveman 2006). Unlike previous economic evaluations in AD, which have based treatment effects on 6 months trial data, this model uses treatment effects estimated on longer term 52 week trial data.

Since patients in the simulation can continue with treatment for an extended period of time, and thus be treated over several severity stages, it was felt inappropriate to model differential treatment effect sizes for mild and moderate AD patients. The simulation therefore applies the same treatment effects for patients initiating therapy over the mild and moderate stages of the disease, with effectiveness estimates in both populations based on pooled data across the spectrum of AD severity. The effect of a reduced treatment effect has been tested extensively in the sensitivity analyses.

NPI was predicted based on four donepezil trials (Winblad 2001b, Feldman 2001, Black 2007, Winblad 2006a) as change from NPI at baseline dependent on treatment, the patient's baseline and most current MMSE and patient characteristics such as race or the intake of psychiatric medication at baseline. More details are presented in the Technical Report and Manuscript (Appendices H, I). The NPI estimates for both treated and untreated patients use the following equation:

$$WorseningFromBaselin\ e_{NPI} = (5.74 - 0.64\,Donepezil + 0.03\,Weeks - 0.59\,NPI_{base} - 0.59\,NPIWeeks + 0.24\,NPI_{recent} - 1.74\,White - 3.82\,Black + 2.34\,PsyMed + 0.12\,MMSE_{base} - 0.22\,MMSE_{recent} + \delta_i) \bullet 1.44$$

Note: Donepezil - treatment effect of donepezil, *Weeks* - weeks of follow-up in the simulation, NPI_{base} is the patient's baseline NPI, NPI_{recent} is the patient's last NPI. *White* and *Black* are dummy variables for race, with the reference groups including "other"; *PsyMed* is a dummy variable for patients on psychiatric medications at baseline (an indication of baseline severity of psychiatric symptoms), $MMSE_{base}$ represents the patient's MMSE at baseline, *Age* represents the patient's age at baseline in years, and $MMSE_{recent}$ represents the patient's previous MMSE. δ_i represents a random intercept parameter, which allows the pattern of decline to vary from one patient to another. The equation was derived based on a normalized scale of 0 to 100, and is therefore multiplied by 1.44 to rescale it to the standard 0 to 144 range for the NPI.

As the equation indicates, changes in NPI are influenced by patients' baseline and most current MMSE. Donepezil's treatment effect, therefore, comes into play not only through the treatment coefficient, but also through its influence on MMSE over time.

For example, for every 1 point benefit on the MMSE due to treatment with donepezil, patients will also be predicted to experience an additional 0.22 point decline in NPI score. There is also an interaction between NPI and time (NPI_{base}Weeks explanatory variable).

Since the scales used to measure function (ADL and IADL) varied in the clinical trials (Winblad 2001b, Feldman 2001, Black 2007, Winblad 2006a, Mohs, 2001), in order to maximize data

availability, standardized scales ranging from 0 (best function) to 100 (worst function) were created, including six basic ADL items (toileting, feeding, dressing, grooming, ambulation, bathing) that were in common amongst the ADL scales selected. These individual item responses were normalized for different response ranges to provide a 0 to 100 scale. The IADL scales all had items in the domains of phone, shopping, food preparation, household tasks, and finances, but only four items were exactly the same in all scales. As such, each trial's IADL scale was taken in its entirety and normalized to 0 to 100.

ADL and IADL change from baseline were also modeled based on treatment, the patient's baseline and most current MMSE and patient characteristics such as race or the intake of psychiatric medication at baseline. For ADL scores, donepezil's effect was modeled directly through the treatment effect term and the terms for patients' most recent MMSE. For IADLs, donepezil's treatment effect comes into play through the treatment term, as well as patients' most recent MMSE and ADL scores. Unlike the other equations, the IADL equation also contains an interaction term between donepezil and time to reflect an increasing effect over time (see Appendix H, I for details).

3.4.7. Treatment Discontinuation

Patients can stop treatment for 3 reasons in the simulation: reaching the end of the user-specified treatment duration (25 years in the base case), clinical stopping rules (MMSE falling below 10 in the base case, according to current NICE guidance), and other unspecified reasons. Patients who stop treatment are assumed to lose all treatment benefits linearly over the course of the subsequent six weeks (Doody et al. 2001).

Baseline hazards of premature discontinuation are applied using data from a UK study of 88 AD patients on donepezil (Lyle et al. 2008). The following recorded causes were included in the hazard calculation: deterioration in cognition or behaviour, physical deterioration, mixed cognitive and behaviour deterioration, mixed cognitive, behaviour and physical deterioration, patient choice and unspecified. As death and discontinuation rules related to disease severity are included in other components of the mode, these reasons for discontinuation were excluded from the hazard calculations in order to avoid double counting. In order to consider individualized predictors of discontinuation of treatment hazard ratios for treatment discontinuation are derived from the all of the available donepezil clinical trial data. These hazard ratios modify the baseline risk of discontinuation derived from the UK observational study, based on patients' initial disease severity, their current disease severity, as well as their most recent rate of progression in disease severity. Based on the baseline hazard and hazard ratios, a time to treatment discontinuation is calculated for each patient actively on treatment.

3.4.8. Survival

Since AD is a chronic condition, this analysis is conducted over a lifetime horizon. The model therefore includes disease specific survival based on age- and sex-specific survival data from a recent large scale UK specific study: the Medical Research Council's cognitive function and ageing study (MRC CFAS 2006; Xie et al. 2008) (Table 10)

Table 10. Median Survival (and Interquartile Range) for 438 Dementia Patients in MRC CFAS

Age (years)	Women	Men
65 to 69	7.5 (4.8-NA)	NA (9.1-NA)
70 to 79	5.8 (3.6-8.3)	4.6 (3.0-8.6)
80 to 89	4.4 (2.8-7.0)	3.7 (2.5-6.3)
≥ 90	3.9 (2.4-5.2)	3.4 (1.5-5.5)

The MRC CFAS data were fitted to functions taking the form: Survival (years) = A x (Percent Surviving)^{B}. Treatment with donepezil was assumed to have no influence on patient survival, so estimates of time to death in the model were assumed to be identical for treated and untreated patients (See Technical Report for additional details, Appendix H).

3.4.9. Valuation of Health Effects

Final health outcomes achieved with treatment are assessed using QALYs. Health utilities for patients were estimated based on a published regression equation (Jonsson et al 2006) which uses EQ-5D with European tariffs to derive health utilities for 272 Alzheimer's patients across the spectrum of cognitive function in Sweden, Denmark, Finland and Norway. Patient demographics in the sample were found to be consistent with patient demographics reported in the UK dementia report (Knapp et al 2007), (see details in Appendix I). The equation was modified to correspond to the full NPI scale as used in the model. Patients across the spectrum of cognitive function were included in the study. The final equation took the form of: EQ-5D Health Utility = 0.408+ MMSE x 0.010 + NPI x -0.004 + Institutionalized x -0.159 + Living with Caregiver x 0.051MMSE represents the patient's current MMSE, NPI represents the patient's current NPI. Institutionalized and Caregiver are dummy variables for whether the patient is institutionalized or lives with their caregiver.

Caregiver utility is based on analysis of donepezil trial data from those trials which measured caregiver quality of life using the SF-36 (Mohs 2001, Winblad 2001b, Feldman 2001). Sf-36 results were transformed into health utilities (see Appendix H) and resulted in equations showing that caregiver utilities were predicted by caregiver age and sex as well as on patient age and disease state parameters based on the following equation:

$$CaregiverU\quad tility\ = 0.90 - 0.003\ Age_{CG} + 0.03\,Male_{CG} + 0.001\ Male_{patient} + 0.00\ MMSE\ - 0.001\ NPI - 0.001\ ADL\ - 0.0004\ IADL\ - 0.01\,PsyMed$$

Note: The coefficient for MMSE is zero, but is included in the equation because the term is included to control for confounding and considered in probabilistic sensitivity analyses, applying a standard error of 0.0007 to the coefficient.

Information was unavailable regarding change in caregiver utility upon institutionalization and therefore not captured in the regression equations. Caregiver utility outcomes are presented separately from patient utility outcomes in the results in order to allow for an assessment of the relative magnitude of effect on QALYs resulting from patient versus caregiver gains.

3.4.10. Resource Use and Costs

Daily treatment costs for donepezil 10 mg of £3.00 have been applied, following a price change effective after the 2009 November Pharmaceutical Price Regulation Scheme. It should be noted that the model assigns the 10 mg cost of donepezil as soon as patients initiate treatment, and there is therefore a slight overestimation of drug costs, since use of the 5mg dose during the titration phase is not considered. Patients on active therapy were also assumed to incur costs associated with additional biannual visits to their physician for monitoring. A cost per visit of £62.29 was assigned based on costs for a geriatrician reported in the National Schedule of Reference Costs 2007-2008 (National Schedule of Reference Costs 2007-2008)(NHS 2009).

As donepezil will lose exclusivity in 2012, a price reduction of 30% and 50% after 1.5 years was assumed to reflect possible market developments. These scenarios were assumed for one-way sensitivity analyses.

Direct health care costs to the NHS and PSS were taken from the Dementia UK report (Knapp et al. 2007) and inflated to 2009 GBP. For patients living in the community, the Dementia UK report provided cost estimates for patients in different severity levels which were interpolated to fit the severity grading used in the model. For institutionalized patients, the Dementia UK report provided only provided a single cost estimate, so that the model applies the same monthly care cost for all patients in institutions regardless of disease severity.

All cost inputs are summarized in Table 11.

Table 11. Cost Inputs

Drug Treatment	Cost per Day	Source
Donepezil 10 mg	£3,00	National Health Service England and Wales (NHS England and Wales 2010)
Monitoring	**Cost per visit**	**Source**
Geriatrician visit	£62.29	National Schedule of Reference Costs (Service Code 430)(NHS Department of Health 2009)
Care costs, living in community	**Cost per month**	**Source**
Mild (≥25)	£687.00	Dementia UK report 2007 (Knapp 2007)
Mild-Moderate (≥20 and <25)	£742.00	Dementia UK report 2007 (Knapp 2007)
Moderate (≥15 and <20)	£798.00	Dementia UK report 2007 (Knapp 2007)
Moderate-Severe (≥10 and <15)	£878.00	Dementia UK report 2007 (Knapp 2007)
Severe (<10)	£957.00	Dementia UK report 2007 (Knapp 2007)
Care costs, institutionalized	**Cost per month**	**Source**
All severity levels	£2,801	Dementia UK report 2007 (Knapp 2007)

Caregiver time was estimated in a linear regression model based on patient characteristics (age, sex) and disease parameters (MMSE, NPI, ADL, IADL, psychiatric medication).

3.4.11 Base Case Analyses

Base case analyses and deterministic sensitivity analyses were based on 20 replications of 1,000 patients in each treatment arm. The analyses were run separately for patients with mild AD (MMSE between 20 and 26) and for patients with moderate AD (MMSE between 10 and 19) as well as for the overall patient population (MMSE between 10 and 26). A full listing of parameter estimates used in the base case analyses is presented in Appendix K.

An alternative base case analysis was run including a 30% and a 50% price reduction after loss of exclusivity after 1.5 years, also for all three patient groups (overall, mild, moderate).

3.4.12. Sensitivity Analysis

For probabilistic sensitivity analyses the model was run 350 times based on runs of 5,000 patients per treatment arm. Probabilistic sensitivity analyses varied the following parameters according to either normal or beta distributions.

- Untreated rates of disease progression as measured by the MMSE
- Treatment effects for donepezil MMSE, NPI, ADL, IADL
- Patient care costs
- Caregiver time regression parameters
- Patient utility regression parameters
- Caregiver utility regression parameters
- Percentage of patients living in the community by disease severity
- Treatment discontinuation rates

For many parameters, standard errors were available from the parameter source data, reflecting the study sampling error. When available, standard errors were used to measure parameter uncertainty. Where a standard error was not available, 95% confidence intervals of ±25% of the mean were assumed to derive standard errors.

Parameters on continuous variables were assumed to be normally distributed, while proportion parameters on discrete variables were generally assumed to be beta distributed. In both cases, the mean and standard errors were used to estimate the distribution parameters.

Estimates for variability used in the probabilistic sensitivity analyses are presented in Appendix K.

Additional scenarios analyses were run to explore effect of changes in the mean of certain parameters on the PSA results.

3.4.13 Results

3.4.13.1 Base Case Results

For the overall population of patients with baseline MMSE scores between 10 and 26, as well as for the mild and moderate population subgroups, donepezil 10 mg dominates the no treatment strategy, with savings from the health care payer perspective ranging from almost £1,900 per patient starting treatment in the moderate stages of the disease (Table 13) to over £3,300 per patient for those starting treatment in the mild stages of the disease (Table 12).

At the same time, QALYs for patients starting treatment with disease of mild severity increase by an average of 0.133, while for those starting treatment with disease of moderate severity, gains are somewhat smaller, averaging 0.098 per patient. Caregiver QALY gains represent roughly 10% of patient QALY gains. When both are considered, donepezil leads to an increase in QALYs of 0.147 per patient with mild disease treated with donepezil, and 0.109 per patient treated with moderate disease.

For patients initiating treatment when their disease is in the mild stages, time alive with MMSE scores above 10 increases by an average of 3.4 months, time with NPI scores above 28, which has been identified as the threshold for serious behavioural disturbances (Tun et al. 2007), falls by 1.2 months, and time institutionalized falls by 2.6 months.

For patients initiating treatment only when their disease has advanced to the moderate stages, benefits are also significant. Time with MMSE scores maintained above 10 increases by over 6 months, largely because a significant number of patients initiate treatment closer to this severity threshold. Time with NPI scores above 28 falls by almost one month, while institutionalization time falls by an average of 1.9 months.

Table 12. Base Case Results for Patients with MMSE ≥ 20 and ≤ 26 versus Untreated Patients (Mild Population)

	Untreated	Donepezil	Net
Survival (undiscounted)	4.110	4.110	0
Drug Costs	£0.00	£2,280	£2,280
Total Costs	**£82,406**	**£79,027**	**-£3,379**
Years with MMSE > 10	2.286	2.573	0.287
Years with NPI < 28	2.226	2.330	0.104
Years with ADL < 50	1.874	2.003	0.129
Years with IADL < 50	0.342	0.432	0.090
Years in Community	1.763	1.981	0.217
Years in Institution	1.919	1.701	-0.217
Total Care Time (Years)	1.469	1.404	-0.065
QALYs (Patient)	**1.370**	**1.502**	**0.133**
QALYs (Caregiver)	2.749	2.764	0.015
QALYS (Patient + Caregiver)	4.119	4.266	0.147
Health Care Direct Cost/QALY (Patient)			**Dominant**
Health Care Direct Cost/QALY (Patient + Caregiver)			**Dominant**

Table 13. Base Case Results for Patients with MMSE ≥ 10 and < 20 versus Untreated Patients (Moderate Population)

	Untreated	Donepezil	Net
Survival (undiscounted)	4.603	4.603	0
Drug Costs	£0	£1,980	£1,980
Total Costs	**£103,964**	**£102,075**	**-£1,889**

	Untreated	Donepezil	Net
Years with MMSE > 10	1.342	1.873	0.531
Years with NPI < 28	2.390	2.472	0.082
Years with ADL < 50	1.546	1.663	0.116
Years with IADL < 50	0.151	0.189	0.038
Years in Community	1.533	1.691	0.159
Years in Institution	2.595	2.436	-0.159
Total Care Time (Years)	1.851	1.804	-0.047
QALYs (Patient)	**1.234**	**1.333**	**0.098**
QALYs (Caregiver)	3.009	3.020	0.011
QALYS (Patient + Caregiver)	4.243	4.353	0.109
Health Care Direct Cost/QALY (Patient)			**Dominant**
Health Care Direct Cost/QALY (Patient + Caregiver)			**Dominant**

When the overall mild to moderate population is considered (Table 14), savings amount to £2,354 and patients gain an average of 0.109 QALYs per patient.

Table 14. Base Case Results for Patients with MMSE ≥ 10 and ≤ 26 versus Untreated Patients (Overall Population, Mild and Moderate)

	Untreated	Donepezil	Net
Survival (undiscounted)	4.458	4.458	0
Drug Costs	£0	£2,071	£2,071
Total Costs	**£97,587**	**£95,233**	**-£2,354**
Years with MMSE > 10	1.622	2.083	0.461
Years with NPI < 28	2.350	2.440	0.090
Years with ADL < 50	1.637	1.758	0.122
Years with IADL < 50	0.208	0.260	0.052
Years in Community	1.602	1.779	0.177
Years in Institution	2.394	2.217	-0.177
Total Care Time (Years)	1.737	1.685	-0.053
QALYs (Patient)	**1.276**	**1.385**	**0.109**
QALYs (Caregiver)	2.932	2.944	0.012
QALYS (Patient + Caregiver)	4.208	4.329	0.121
Health Care Direct Cost/QALY (Patient)			**Dominant**
Health Care Direct Cost/QALY (Patient + Caregiver)			**Dominant**

3.4.13.2. One Way Sensitivity Analyses

One way sensitivity analyses were conducted for the mild and moderate patient populations. They indicate that donepezil's position of dominance held in both population subgroups in almost all analyses, with broadly similar results for both population subgroups. Results were most strongly influenced by reduction in the costs of caring for patients in the severe stages of AD, particularly those costs associated with nursing home care. For the group initiating treatment with disease of moderate severity, a reduction in inputs related to all costs of care (monthly direct costs in community and institution) of 50% resulted in an ICER of £1,370/QALY. When nursing home costs alone were reduced by 50%, the ICER was £7,093/QALY (Table 16). In the mild patient group, only the reduction of nursing home costs by 50% moved donepezil from a position of dominance to an ICER of £1,866/QALY (Table 15). These results demonstrate that although donepezil leads to a modest reduction in the average time patients spend in nursing homes or with severe disease (i.e., MMSE < 10), the high costs associated with this stage of the disease are an important determinant of economic outcomes.

The analyses run with a shorter time horizon and shorter treatment duration indicate that almost all costs and benefits occur within the first five years of the analysis, as both cost and QALY results are largely similar to those run using a 25 year time horizon. The same applies to analyses run using a full time horizon, but a shorter treatment duration. This is because most patients will have either reached the severe stages of the disease, died, or discontinued treatment over the first 5 years of the simulation.

The model applies the same treatment effect over time for both mild and moderate patients. Previous models have assumed a smaller treatment effect in patients starting therapy while in the mild stages of the disease. However, in sensitivity analyses show were treatment effects in this population are reduced by 50%, donepezil still leads to an improvement in QALYs and reduced overall costs.

While donepezil was dominant in the remaining analyses, a strong influence can be observed from changes in the baseline rate disease progression and treatment effect estimates as well as from the variation of discontinuation rates. In the last case, however, both QALY gains and savings change relatively proportionally with alternative discontinuation rate inputs.

In multi-way analyses, donepezil remained dominant in the mild population when both costs of care in community and treatment effects were reduced by 25% and nursing home costs were reduced by 30% simultaneously, although savings decreased to just below £100 and QALY gains

amounted to only 0.077 per patient for patients starting treatment during the moderate stage of the disease.

Allowing treatment to continue when MMSE scores fall below 10 led to an increase in QALYs gained, but because no cost offsets over this stage of the disease are considered using current model assumptions, overall savings per patient fell.

Table 15. One Way Sensitivity Analysis Results for All Patients with MMSE ≥ 20 and ≤ 26: Donepezil versus Untreated Patients (Mild Population)

Analysis	Net QALYs*	Net Direct Cost	Cost/QALY*
Base Case	**0.147**	**-£3,379**	**Dominant**
3-Year Time Horizon	0.108	-£2,382	**Dominant**
5-Year Time Horizon	0.142	-£3,255	**Dominant**
Discount Rate: 0% for both Cost and Health	0.159	-£3,650	**Dominant**
Discount Rate: 0% Cost, 6% Health	0.140	-£3,650	**Dominant**
Discount Rate: 6% Cost, 0% Health	0.159	-£3,202	**Dominant**
Discount Rate: 6% for both Cost and Health	0.140	-£3,202	**Dominant**
[1] MMSE Progression ↓ 25%	0.181	-£4,443	**Dominant**
[1] MMSE Progression ↑ 25%	0.117	-£2,332	**Dominant**
[2] Treatment Effect MMSE ↓ 25%	0.109	-£1,840	**Dominant**
[2] Treatment Effect MMSE ↓ 50%	0.070	-£213	**Dominant**
[3] Treatment Effect (All) ↓ 25%	0.107	-£1,840	**Dominant**
[3] Treatment Effect (All) ↓ 50%	0.066	-£213	**Dominant**
[4] Discontinuation ↓ 50%	0.176	-£4,054	**Dominant**
[4] Discontinuation ↑ 50%	0.123	-£2,808	**Dominant**
Treatment Duration 3 years	0.108	-£2,391	**Dominant**
Treatment Duration 5 Years	0.142	-£3,257	**Dominant**
No Stopping When MMSE =0	0.155	-£2,980	**Dominant**
[5] % in NH ↓ 25%	0.136	-£2,221	**Dominant**
[6] Costs of Care ↓ 25%	0.147	-£1,904	**Dominant**
[6] Costs of Care ↓ 50%	0.147	-£430	**Dominant**

Analysis	Net QALYs*	Net Direct Cost	Cost/QALY*
[7] Costs of NH ↓ 25%	0.147	-£1,552	**Dominant**
[7] Cost of NH ↓30%	0.147	-£1,187	**Dominant**
[7] Costs of NH ↓ 50%	0.147	£275	**£1,866/QALY**
[8] Patient QALY Effect ↓ 50%	0.104	-£3,379	**Dominant**
[8] Caregiver QALY Effect ↓ 50%	0.140	-£3,379	**Dominant**
[9] Cost of MD Visit ↑ 50%	0.147	-£3,259	**Dominant**
[10] Cost of Care ↓ 25% (NH ↓ 30%) and Treatment Effect (All) ↓ 25%	0.107	-£493	**Dominant**
[11] Cost of severe equals to cost of moderate-severe	0.147	-£3,297	**Dominant**
[12] Donepezil Price ↓ 30% after 1.5 years of treatment	0.147	-£3,744	**Dominant**
[12] Donepezil Price ↓ 50% after 1.5 years of treatment	0.147	--£3,988	**Dominant**
5-year time horizon with no discounting and no discontinuation	0.217	-£5,006	**Dominant**

Table 16. One Way Sensitivity Analysis Results for All Patients with MMSE ≥ 10 and ≤ 20: Donepezil versus Untreated Patients (Moderate Population)

Analysis	Net QALYs*	Net Direct Cost	Cost/QALY*
Base Case	**0.109**	**-£1,889**	**Dominant**
3-Year Time Horizon	0.100	-£1,677	**Dominant**
5-Year Time Horizon	0.109	-£1,883	**Dominant**
Discount Rate: 0% for both Cost and Health	0.115	-£2,019	**Dominant**
Discount Rate: 0% Cost, 6% Health	0.105	-£2,019	**Dominant**
Discount Rate: 6% Cost, 0% Health	0.115	-£1,802	**Dominant**
Discount Rate: 6% for both Cost and Health	0.105	-£1,802	**Dominant**
[1] MMSE Progression ↓ 25%	0.144	-£2,776	**Dominant**
[1] MMSE Progression ↑ 25%	0.086	-£1,424	**Dominant**
[2] Treatment Effect MMSE ↓ 25%	0.080	-£983	**Dominant**
[2] Treatment Effect MMSE ↓ 50%	0.052	-£48	**Dominant**
[3] Treatment Effect (All) ↓ 25%	0.077	-£983	**Dominant**
[3] Treatment Effect (All) ↓ 50%	0.047	-£48	**Dominant**
[4] Discontinuation ↓ 50%	0.125	-£2,238	**Dominant**
[4] Discontinuation ↑ 50%	0.096	-£1,599	**Dominant**
Treatment Duration 3 years	0.100	-£1,680	**Dominant**
Treatment Duration 5 Years	0.109	-£1,883	**Dominant**
No Stopping When MMSE =0	0.127	-£726	**Dominant**
[5] % in NH ↓ 25%	0.101	-£1,104	**Dominant**
[6] Costs of Care ↓ 25%	0.109	-£870	**Dominant**
[6] Costs of Care ↓ 50%	0.109	£150	**£1,370/QALY**
[7] Costs of NH ↓ 25%	0.109	-£557	**Dominant**
[7] Cost of NH ↓30%	0.109	-£291	**Dominant**
[7] Costs of NH ↓ 50%	0.109	£775	**£7,093/QALY**
[8] Patient QALY Effect ↓ 50%	0.077	-£1,889	**Dominant**
[8] Caregiver QALY Effect ↓ 50%	0.104	-£1,889	**Dominant**

Analysis	Net QALYs*	Net Direct Cost	Cost/QALY*
[9] Cost of MD Visit ↑ 50%	0.109	-£1,785	**Dominant**
[10] Cost of Care ↓ 25% (NH ↓ 30%) and Treatment Effect (All) ↓ 25%	0.077	£91	**£1,172/QALY**
[11] Cost of severe equals to cost of moderate-severe	0.109	-£1,738	**Dominant**
[12] Donepezil Price ↓ 30% after 1.5 years of treatment	0.109	-£2,117	**Dominant**
[12] Donepezil Price ↓ 50% after 1.5 years of treatment	0.109	-£2,270	**Dominant**
[13] 5-year time horizon with no discounting and no discontinuation	0.150	-£2,793	**Dominant**

* Patient and caregiver QALYs

[1] Reduction/increase of MMMS change by 25%, applied to intercept in MMSE change equations

[2] Reduction of treatment effect on MMSE by 25%, 50%

[3] Reduction of treatment effect on all disease progression scales (MMSE, NPI, ADL, IADL) by 25%, 50%

[4] Reduction/increase of discontinuation rate by 50%

[5] Reduction of the percentage of patients institutionalized by 25%

[6] Reduction of the costs of care in community and nursing homes by 25%, 50% (excludes costs of donepezil or medical visits associated with use of donepezil)

[7] Reduction of nursing home costs by 25%, 50%

[8] Reduction of the effect of MMSE, NPI, ADL and IADLs on patient/caregiver QALYs by 50%

[9] Increase of costs for physician visits associated with use of donepezil by 50%

[10] Simultaneous reductions of costs of care in community by 25% and costs of care in nursing homes by 30% and treatment effects on all scales (MMSE, MPI, ADL, IADL) by 25%

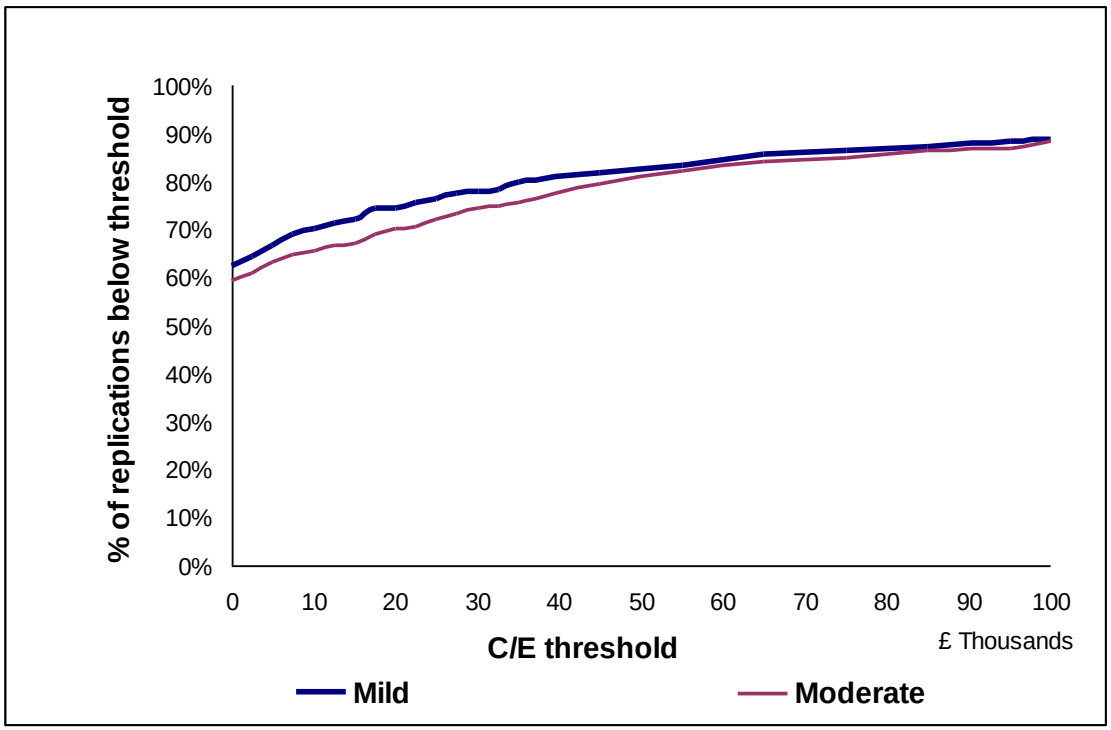
[11] Total costs of care for patients with severe disease are set as equivalent to those for patients with moderately-severe

[12] Reduction of the price of donepezil of 30%, 50% assumed after 1.5 years

3.4.13.3. Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses yielded considerably more variability in outcomes. Figure 3 shows the cost-effectiveness acceptability curves for donepezil versus no treatment for the subgroup of patients starting treatment with mild and moderate disease severity respectively. The incremental cost per discounted QALY estimates fall below £30,000 in 78% of replications for the mild population, and in over 74% for the moderate population. For patients initiating treatment with disease of moderate severity, 70% of replications result in cost per QALY estimates below £20,000/QALY, as do more than 74% in the mild patient population.

Figure 2. CEAC Curves for Donepezil versus No Treatment in the Mild and Moderate Patient Populations



The scatterplots confirm that in both populations the majority of replication results in both QALY gains and lower costs (Figure 3 and 4). In the PSAs, mean savings of -£1,817 and mean QALY gains of 0.129 were obtained in the mild population, while in the moderate population mean savings of -£1,361 and mean QALY gains of 0.104 were generated. The PSA results may over represent uncertainty because of uncorrelated sampling from input probability distributions and because of conservative assumptions on the degree of variability in inputs where direct estimates were unavailable (see Appendix H for details). This is evidenced by the fact that in a small minority of cases, QALYs are estimated to be higher in the untreated versus the treated population.

Figure 3. PSA Cost-effectiveness Results in the Mild Patient Population

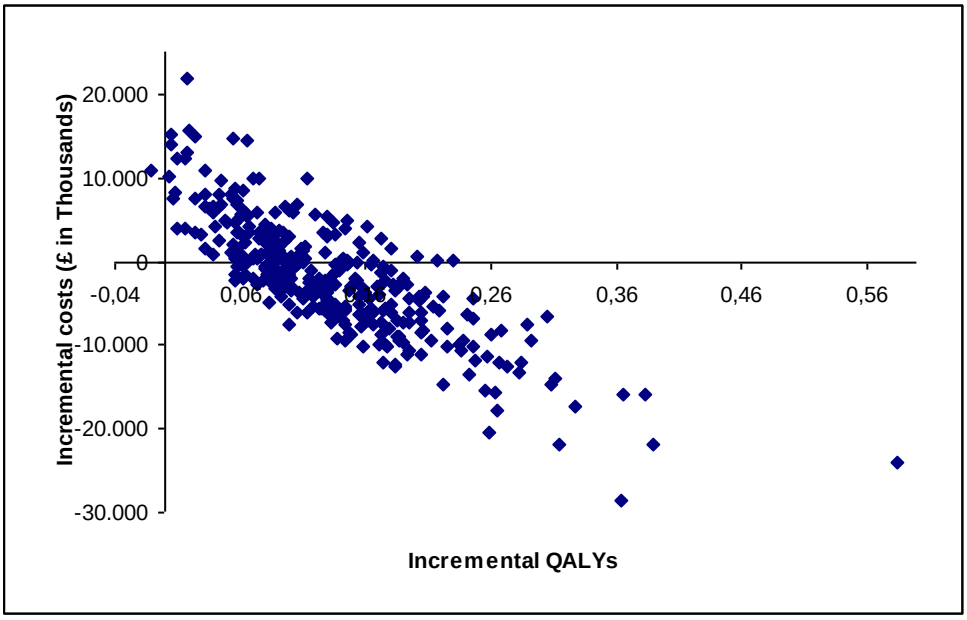
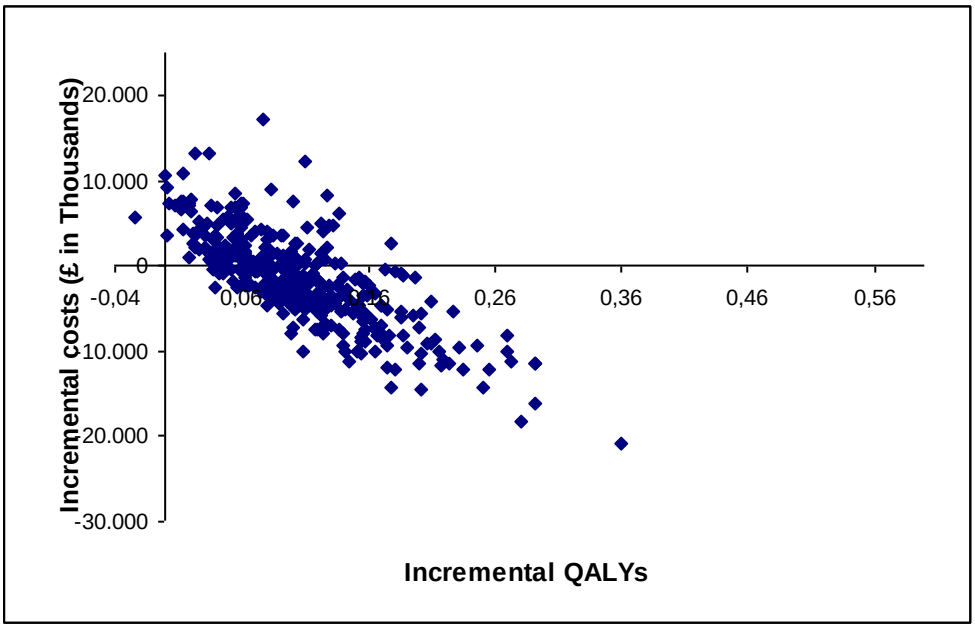


Figure 4. PSA Cost-Effectiveness Results in the Moderate Patient Population



A probabilistic sensitivity analysis was also performed for the scenario in which costs of care and treatment effects were reduced simultaneously by 25% and nursing home costs were reduced by 30%. In the mild patient population, over 63% of replications produced ICERs below £20,000, and in 70% of replications, the ICER fell below £30,000. For patients initiating treatment with moderate AD, over 58% of replications result in cost per QALY estimates below £20,000, and

66% in ICER estimates below £30,000. Under these settings, the probabilistic analyses yielded small incremental costs for both mild and moderate patients, with incremental costs averaging £249 per patient initiating treatment while there disease was in the mild stages and £354 per patient initiating treatment with moderate disease. Mean QALY gains were also lower, at 0.094 and 0.074 for mild and moderate patients respectively. Mean ICER's, however, were only £2,647 and £4,791 for the mild and moderate populations.

3.4.14 Interpretation of the Economic Evidence

The results of the analyses indicate that donepezil is clearly cost-effective in the treatment of patients in both stages of mild and moderate AD. The analyses indicate donepezil would not only dominate treatment without pharmacotherapy in both subgroups, but also that treatment of patients with mild disease would offer significant additional health benefits and savings. Results underline that both monetary savings and QALY gains are more pronounced the earlier treatment is initiated, which is in line with findings from recent clinical evidence (Molinuevo 2009). Early onset of treatment can delay progression to severe disease (i.e., MMSE < 10), and the high costs associated with this stage of the disease are an important determinant of economic outcomes. More importantly, significant QALY gains and cost offsets can be attained by delaying progression of AD, even before patients reach the most severe stages of the disease.

Probabilistic analyses incorporating parameter uncertainty reflect some degree of uncertainty, but they confirm that even with zero willingness to pay for a QALY, donepezil is a cost-effective option with a high probability in both mild and moderate AD patients. At any positive willingness to pay for a QALY, donepezil has a very high chance of being cost-effective, compared to no treatment.

Extensive one-way sensitivity analyses confirmed that results are robust to changes in parameters. Donepezil remains dominant or highly cost-effective in both mild and moderate AD patients under various assumptions – results were consistently in favour of donepezil. The one-way sensitivity analyses allow other conclusions too. First, even though the time horizon of the analysis was set to be 25 years to capture all possible costs and health benefits, the analyses run with a shorter time horizon and shorter treatment duration indicate that almost all costs and benefits occur within the first three to five years of the analysis since most patients will have either died, reached the severe stages of the disease or discontinued treatment by this point. Cost neutrality is achieved by 6 month into treatment, and 90% of the cost savings occur in the first 3 years of treatment. This is clearly important in light of the evidence that average treatment duration is likely to be less than 5 years.

Donepezil is initiated in mild and moderate AD patients, and in line with its licence, it may be continued as long as benefit is experienced. Potentially, this includes cases where the patient becomes severe. The analysis in which the stopping rule of MMSE<10 is suspended resulted in higher patient QALYs but also higher costs. On average this scenario still reported cost savings, albeit considerably smaller. Potentially, this finding could support continuous treatment of AD patients even though they progress to more severe disease stages. As the analyses presented here assume the costs for all patients in the severe stages of the disease are identical, with no potential for any cost offsets with continued treatment, they are not well equipped to properly assess whether treatment after MMSE falls below 10.

In line with previous NICE assessments the presented model only compares cost effectiveness against no treatment. As described under Section 3.4.3 comparisons between the different AChEIs are not considered due to very limited clinical evidence supporting the differentiation between the treatments (Birks 2006, Ritchie 2004, Hansen 2008, Rainai 2008). Galantamine, rivastigmine and donepezil have been found to have similar efficacy in terms of cognition, with donepezil and rivastigmine showing a dose effect across studies (Ritchie 2004) Fewer adverse events appear to be associated with donepezil as compared to rivastigmine (Birks 2006). A systematic review came to conflicting results, with some of the reviewed studies showing no differences in efficacy between donepezil, galantamine and rivastigmine, one study found donepezil to be more efficacious than galantamine, and one study found rivastigmine to be more efficacious than donepezil. Conducted indirect comparisons did not yield statistically significant differences regarding cognition, but found a better relative risk of global response with donepezil and rivastigmine as compared to galantamine and also favored donepezil over the two comparator drugs with regard to behaviour (Hansen 2008). Another systematic review by Rainai and colleagues found no differences in cognition and behaviour in studies that compared different AChEIs (Rainai 2008).

Although there are small differences in treatment prices, an economic comparison would need to consider not only drug prices, but the differing burden of staff cost for initiation and monitoring patients during titration to a maintenance dose. Both rivastigmine and galantamine are started at non-efficacious doses requiring multiple-titration involving multiple clinic visits. Donepezil in contrast is started at an efficacious dose with only one titration step for once daily maintenance. Furthermore, with the pending loss of exclusivity for these products, price changes will diminish even further. Indeed, in an analysis of a 30% reduction in the price of donepezil after 1.5 years on treatment indicates 20% greater cost-savings for mild AD and 31% greater cost-savings in moderate disease, compared to the current base case analyses.

In the economic analyses that supported the current guidance to restrict treatment to patients in the moderate stage of AD the cost-effectiveness of treatment initiated while patients were still in the mild stages of the disease was estimated to be above currently accepted thresholds of £20,000-30,000 per QALY. The analyses presented here indicate that use of donepezil would result in savings. Further, both savings and health benefits are expected to be even greater for mild patients.

There are a number of reasons why the results presented here differ significantly from those conducted on behalf of NICE in TA 111, published in 2006 (Loveman 2006), including from the final results presented in the Final Appraisal Determination in 2009 (NICE 2009). The limitations of the models used by NICE to evaluate the cost-effectiveness of AChEIs in the past have been documented by,NICE and the model used in this analysis attempts to overcome some of those limitations.

One of the important differences is that our analyses apply measurements of disease progression on a series of continuous scales – MMSE, NPI, ADL, and IADL – as opposed to the model used by NICE for the TA 111 (NHS England and Wales 2009) which dichotomized AD into requiring full time care and not requiring full time care. Accordingly, in our analyses both health utilities and costs are tracked with much greater precision. This has important implications as the DES allows us to capture benefits over the full course of the disease and to account for even relatively small changes in disease progression and their consequences.

While our results are not directly comparable to those conducted on behalf of NICE, both models predict delays in reaching severe stages of the disease of roughly 1.5 to 3 months, while total cost and benefit results differ significantly, suggesting that the ability to capture finer gradients of benefit over the course of the disease has a large impact. In the model analyses conducted for NICE, the mean delay to requiring full-time care for donepezil was approximately 2 months. In our analyses, the requirement for full time care is not modeled as an outcome, but the reduction in time patients spend institutionalized is roughly 2.5 months. These estimates are in line with previous modeling efforts which suggest that the delay to institutionalization or full time care is less than 6 months. The difference in ability to capture benefits over the entire course of the disease has implications not only for the assignment of costs in the model, but also health utilities. QALY gains for patients on donepezil averaged 0.11 per patient. In both the NICE model and the original AHEAD model (used as the basis for the model used by NICE) used to evaluate the cost-effectiveness of galantamine (Loveman 2006, Ward et al. 2003), QALY gains per patient were lower, averaging about 0.06 per patient.

Another important difference between the models is the incorporation of longitudinal multivariate analyses of disease progression and treatment effects, with treatment effects based on up to one

year of placebo-controlled data in our model. The predictions from the multivariate regression analyses for untreated patients have been compared to expected cognitive outcomes in the CERAD population and provided good fits. Similarly, treatment effect sizes at 6 months, the duration of most of the clinical trials, in the simulated population were very close to those observed in the trials (See Appendix Table 7 in the Appendix I Manuscript). For example, mean treatment effect at 24 weeks in MMSE and NPI are -1.92 and 1.75 respectively, very close to the mean observed treatment effect of -1.88 and 1.68 (for further details see Appendix I Manuscript).

The analyses conducted on behalf of NICE applied only a fixed mean treatment effect across patients over a single time interval, whereas the DES allows for treatment effects to vary over time. Unlike the NICE model, our model does not apply an undifferentiated and constant mortality risk, includes stopping rules, considers less than perfect persistence with treatment, and integrates caregiver health directly into the model rather than applying it post-hoc based on calculations largely external to the model. By using DES and sampling from patient level data sets to create simulated patients, we were also able to create a much more realistic sample of individuals with demographic and disease characteristics that reflect observed data, rather than sampling from a selection of uncorrelated distributions.

Our simulation also used different data sources than those used in the NICE evaluation, which could also explain differences in results between the two models. For example, the NICE evaluation assumed that only 70% of costs associated with institutionalization would be covered by the National Health Service, and therefore only included 70% of institutional care costs in their analysis. We used the full cost of institutional care in our base case analyses, but in sensitivity analyses where we reduced this cost by 30%, donepezil remained dominant. Data for health utilities, costs of care, institutionalization and patient profile inputs, all differ between the two models. The results of our sensitivity analyses, however, which indicate that varying these inputs over wide ranges does not substantively alter findings, suggest that it is the differences in modeling techniques and assumptions which has a far greater impact on results than differences in the selection of input data. This finding coincides with conclusions from the Gustavsson (2009) study.

Limitations of the data revolve around assigning costs and utilities associated with different degrees of disease severity. In particular, the cost data for the UK are based entirely on MMSE ranges and do not consider behaviour or function. Using the current model inputs, behavioural symptoms as measured by the NPI, do not influence costs, although they do have a direct impact on caregiver time, as well as on both patient and caregiver utilities. ADLs and IADLs have an effect only on caregiver time and utilities in the current analyses. While it is likely that ADLs and

IADLs do impact patient utilities and costs, in the absence of a good data source this is not considered in the model, therefore potentially underestimating the benefits of treatment.

The costs associated with the management of co-morbidities in AD patients have not been explicitly accounted for in our economic model. These costs have been shown to be substantially higher than for AD patients with no co-morbidities (Hill et al., 2002a). Higher costs have been attributed to the higher inpatient and skilled nursing facility costs and the duration of hospital stays, that is longer for patients with a diagnosis of dementia than for those without (Sebestyen et al. 2006; Wancata et al. 2001). Improving the cognitive and behavioural symptoms of AD can lead to more effective and cost-effective management of co-morbid conditions in AD patients, at least in part because of improved adherence to therapy for the co-morbid condition and consequently a reduced need for additional intervention (Hill 2002b). Thus, improving the symptoms of AD and delaying its progression from the early to the more advanced stages of the disease may not only reduce the burden and costs associated with AD itself but also the differential burden (between AD and non-AD patients) that results from the management of co-morbid conditions. Therefore the model may be under-estimating the cost-effectiveness of donepezil by assigning costs based on MMSE scores only, and not accounting for other aspects of disease severity such as function and behavior.

Further, in order to achieve a finer gradient of costs, we interpolated the cost of care for patients living in the community, creating costs for five severity ranges, based on source data for three ranges. Whether there is a linear relationship between costs and severity for patients with mild, moderate and severe cognitive decline could not be evaluated from the available data, and therefore introduces uncertainty in our estimates. Health care costs for patients living in the community, however, are much less influential than estimates associated with the costs of care for institutionalized patients. Nursing home costs are a key driver of cost outcomes in the model. Unfortunately, given available data institutionalization costs are assumed to be the same for all patients regardless of disease severity, so the simulation does not capture any cost offsets to treatment over this phase of the disease.

The predictive equations developed for this model have not been validated against external data sets. As mentioned above, simulated and observed cognitive outcomes and treatment effects fared well against clinical observations. The CERAD and trial data, however, were used to develop the equations themselves, and therefore do not provide the strongest test of the validity of the equations. In sensitivity analyses, even when treatment effect terms were reduced by 50%, donepezil remained dominant in patients both with mild and moderate disease. Furthermore, sensitivity analyses on key parameters, including the overall rate of change for MMSE using the CERAD equations, indicated that results were consistently favourable for donepezil. Nevertheless

validation against a dataset not used to develop the equations would be required for more robust testing and refinement of the equations. The predicted effects of donepezil are based on clinical trial data and it is possible that treatment effectiveness would be different in actual practice. The probabilistic sensitivity analyses were also subject to a number of limitations. In some cases, variance figures around estimates were unavailable, and a standard error of 25% of the mean was assumed. The analyses also did not consider potential correlations between parameters in the disease progression equations. Another limitation of the current analyses stems from the fact that the source files used to assign population characteristics is based on a clinical trial population. Although we attempted to simulate a population more applicable to the UK by ensuring that the age and gender distribution of simulated patients was equivalent to that of the UK population with AD, the approach would not have controlled for all differences between the trial population and the actual UK AD population. For example, in the current simulations, patients initiating treatment over the moderate stages of the disease are predicted to survive slightly longer, on average, than patients initiating treatment over the mild stages of the disease. This is because the simulated population with moderate disease is slightly younger than the population with mild disease, and has a larger proportion of females. To control for this, we would have required data the age and gender profile of AD patients in the UK with different severity strata. Shorter survival among patients with mild AD is likely to cause underestimation of benefits for these patients, given that patients living longer would have longer time to accumulate benefits from treatment, which would result in greater savings and more favourable results. This inaccuracy is unlikely to bias results in favour of donepezil, as baseline characteristics and survival are identical for treated and untreated patients in the simulation, although it should be noted that longer survival in patients with mild disease would likely lead to improved results, as it would allow for a larger number of untreated patients to progress to the most severe stages of the disease.

While the model does still capture health benefits when patients progress to severe disease stages, it assumes the same cost of care for all patients, so that potential cost offsets of continued treatment in severe disease stages could not be adequately captured and would therefore be underestimated

The overall conclusion from the model is that donepezil treatment produces cost savings to the NHS and personal social services while results in greater benefit to patients compared with usual care alone. Even where the base case results are most sensitive to variations in variables such as nursing home costs, the resulting incremental cost effectiveness ratios are well within the accepted cost-effectiveness thresholds. The cost effectiveness of donepezil in both mild and moderate AD populations would further improve when patent is lost and generic donepezil is available at significantly lower prices than the current branded list price.

SECTION 4 WIDER IMPLICATIONS TO THE NHS

4.1 Executive Summary

- AChEIs in general and donepezil in particular are already widely used among patients with mild and moderate AD who are diagnosed and referred to specialist clinics reflecting the value clinicians place upon the value of symptomatic management.
- Compared with current levels of spending, the impact of a recommendation in mild disease for donepezil is estimated to result in an increase in England and Wales of £5.7 million in 2011 and £6.8 million in 2015 in the expenditure on AChEIs.
- However, the additional drug expenditure associated with a mild AD recommendation for donepezil is estimated to be offset by savings resulting from the effect of donepezil in delaying institutionalised care costs. The estimated net budget impact of a donepezil mild AD recommendation is net savings of £1.6 million in 2011 and £4.7 million in 2015 across England and Wales. Seen another way, if the NICE guidance remains as a recommendation for donepezil in moderate AD patients only, then this will cost the NHS in England and Wales an additional £1.6 to £4.7 million between 2011 and 2015. With a mild AD recommendation for donepezil, costs of institutionalisation are expected to decrease by £8.1 million in 2011 and £12.81 million in 2015 whereas non-institutionalised care costs are expected to increase by £0.84 million in 2011 and £1.32 million in 2015.
- Recommending donepezil for mild AD patients in addition to the current recommendation for moderate AD patients is estimated to result in savings even when key parameters are varied such as rates of patient diagnosis, referral and subsequent treatment. Drug compliance has a limited effect on total cost implications.
- All the above health economic and budget impact calculations are based on the current list price for donepezil which has been reduced by 5.8% since the last guidance. It should be noted however that donepezil will lose patent protection in the UK in February 2012 when several generic versions will become available at a significantly reduced cost (we are aware of a number of generic license approvals to date). Uncertainty concerning the exact generic price post loss of patent should not mean that this fundamental factor is discounted and Eisai/Pfizer are prepared to discuss with NICE guaranteeing a donepezil price post patent expiry in order that the effect of this can be included in health economic modeling approaches.

4.2 NHS Budget Impact between 2011 and 2015

This section estimates the budget impact on the NHS in England and Wales between 2011 and 2015 of a NICE recommendation for donepezil for mild in addition to moderate AD patients, as currently recommended. Budget impact estimates exclude the impact of a change in NICE guidance for any of the other AChEIs or memantine. Budget impact estimates exclude the impact of a change in NICE guidance for any of the other AChEIs or memantine.

4.2.1 Methods

A simple prevalence based budget impact model was built to synthesize epidemiology data from the literature, market research data on the use of donepezil in mild and moderate AD patients to estimate additional costs and savings to the NHS in England and Wales over a 5 year period of a change in the NICE guidance.

The proportion of patients with dementia is expected to increase by 154% from 2006 to 2021 (Knapp et al 2007, Dementia UK). Taking into account the increase in population from 2006 to 2051 this translates into an annual increase of 1.11% in the proportion of patients with dementia, from 1.3% in 2010 to 1.37% in 2015.

The population in England and Wales in 2011 is estimated to be 55.6 million, with estimates of the population reaching 57.2 million in 2015 (Office of National Statistics 2009). Of all patients with dementia, the proportion of patients with AD is 60% (Luengo-Fernandez 2010). This proportion is assumed to remain constant over the next 5 years.

Estimates of the proportion of mild, moderate and severe patients with AD were taken from the Dementia UK report and were assumed to be 55.4%, 32.1% and 12.5% respectively (Knapp et al 2007, Dementia UK). The distribution is also assumed to be constant over time.

There are varying estimates in the literature of the proportion of prevalent patients who get diagnosed. Age specific diagnosis rates in Knapp et al 2007 are higher than the diagnosis rate in the most recent report by Luengo-Fernandez 2010. To be conservative, in the base case the model includes the assumption that 47.3% of prevalent patients are fully diagnosed, calculated using the Dementia diagnosis proportion estimates from the NAO (2007). Based on a linear interpolation between the data points for the age-groups 65-69 to 80 provided in the report, an overall diagnosis rate was obtained using the weighted average of age groups (see Table 17 below).

Alzheimer's patients are assumed to have the same diagnosis rate as the wider population of dementia patients, and the proportion is assumed to be equivalent for both mild and moderate AD

patients. Sensitivity analysis is used to explore the uncertainty around diagnosis rates by varying the rate from 33% to 57% to capture the full variation in the literature.

Table 17. Number of People with Dementia and Proportion Diagnosed by Age Group

Age group	Number of prevalent patients with dementia	Prevalence within age groups	Proportion of prevalent patients diagnosed
65-69	33,651	1.3%	38.5%
70-74	63,695	2.9%	41.7%
75-79	114,821	5.9%	45.3%
80+	456,399	19.5%	49.2%

From among the number of patients diagnosed, only a limited number of patients are referred to specialists. Very limited data is available on proportion of patients diagnosed who are then referred on to a specialist. Data on referral rates to a Southampton memory clinic in 2004 estimated the overall referral rate for mild and moderate patients to be 68% and this rate was used for the first year in the 5 year time period (2010). Separate referral rates for mild and moderate AD patients were required to estimate the budget impact of a recommendation for mild AD patients. These separate rates were calculated by adjusting the average referral rate from the Southampton study by the current relative proportions of mild and moderate disease. This approach resulted in a base case 60% referral rate for mild patients and an 85% rate for moderate AD patients. The rate of referral for mild AD patients would be expected to increase as a result of a change in NICE guidance to recommend donepezil for mild AD patients, whereas the rate for moderate patients would not change over time. The referral rate was assumed to grow by 1% per annum for mild AD patients, increasing to 64% by 2015, while no change was assumed for moderate patients.

Based on 2009 data from Dementia Trak (McLeod 2009) 78.1% and 91.2% of the mild and moderate AD patients referred to specialists are currently treated. The figure for mild patients is assumed to increase to 91.17% patients in 2011 based on a positive NICE recommendation for donepezil. This assumption is tested in the sensitivity analysis. Out of the treated patients 93% received AChEIs or memantine among both mild and moderate patients – with the rest of the patients taking neuroleptics – and this value is assumed to be constant over time. The market share of donepezil among AChEIs and memantine is estimated to be approximately 63.4% in mild AD patients and 61.8% in moderate disease, based on 2009 market share data from

Dementia Trak (McLeod 2009). The market share of donepezil treatment is assumed to remain constant for the time period of the budget analysis.

To be conservative, no treatment discontinuation has been taken into account in the base case, but its impact is tested in sensitivity analysis. The literature estimates of compliance with donepezil at one year vary significantly. Winblad et al. (2001) estimated that only 7% of donepezil patients discontinue treatment due to adverse events. Similarly Doody et al. (2009) found that approximately 10.3% of patients discontinued treatment due to adverse events. However Lyle et al (2008) found that 57.9% of donepezil treated patients remain on treatment after 1 year. A sensitivity analysis was run assuming 80% compliance, which was based on the average of the three estimates in the literature, translating into a monthly reduction of 1.65%((1-0.579)+0.07+0.103) / (3 * 12) of patients initiating treatment at the beginning of the year.

Daily treatment costs for donepezil 5mg of £2.14 and 10mg of £3.00 have been used in the model, taking into account the price change effective after January 1st 2010 based on the Pharmaceutical Price Regulation Scheme http://www.ppa.org.uk/edt/March_2010/mindex.htm. The costs for donepezil in the model are based on the assumption that patients are treated with 5mg dose for one month but then titrate up to 10mg as recommended in SPC (2009).

The branded version of donepezil (Aricept) will lose patent exclusivity in February 2012 so it is anticipated that a generic version will be distributed from this time onwards. Based on company forecasts approximately 81% of the donepezil sales are expected to come from generic donepezil from February 2012. In the base case estimates, the list price of Aricept is assumed to apply for the first year of the model (2011-2012) but thereafter a generic donepezil is assumed to be used at a 30% lower price from 2012 onwards. As generic donepezil is expected to be available at much lower prices than that assumed in this model, this is a conservative scenario, which may over-estimate the budget impact.

Besides drug costs, savings associated with the use of donepezil are considered in the model. Drug treatment in AD patients has been shown to delay institutionalisation, therefore, the savings in direct health care costs by the location of care (nursing home and home costs) were included in the model only for mild AD patients who would have been untreated but who now receive treatment under a positive NICE recommendation. The annual nursing home and home care costs were taken from the cost-effectiveness model described in the previous section. The estimates were obtained by running the cost effectiveness model for a 5 year time horizon, assuming no discounting and no discontinuations. Costs in the cost-effectiveness model are shown to increase linearly, therefore the estimated costs per patient over 5 years were divided into equal annual estimates and factored into the budget impact model as annual costs.

4.2.2 Results

Table 18 shows the estimated number of patients formally diagnosed with AD from 2011 to 2015. The estimated number of diagnosed Alzheimer patients is 207,498 in 2011 and 223,590 in 2015.

Table 18. Number of Diagnosed Patients over Time

	2011	2012	2013	2014	2015
Total population of England and Wales	55,601,320	55,993,805	56,387,650	56,781,482	57,175,515
Proportion with dementia	1.32%	1.33%	1.35%	1.36%	1.38%
	731,186	745,009	759,074	773,366	787,893
Proportion with Alzheimer dementia	60%	60%	60%	60%	60%
	438,712	447,005	455,444	464,020	472,736
Proportion with AD formally diagnosed	47.30%	47.30%	47.30%	47.30%	47.30%
	207,498	211,420	215,412	219,468	223,590

Table 19 provides estimates of the number of mild patients eligible for treatment with the projected market following a change in guidance as well as with the projected market based on the current guidance. If the guidance remains unchanged the estimated number of mild AD patients on donepezil treatment will be 28,860 in 2011 and 33,171 in 2015. If the guidance would alter to recommend the use of AChEIs in mild patients the estimated number of patients on donepezil treatment would increase by 8,090 in 2011 and 9,299 in 2015.

Table 19. Patients with Mild AD on Treatment with Current NICE Guidance

	2011	2012	2013	2014	2015
Proportion of diagnosed AD patients with mild disease [1]	55.40%	55.40%	55.40%	55.40%	55.40%
	114,954	117,127	119,338	121,585	123,869
Proportion referred to specialists [2]	60%	61%	62%	63%	64%
	68,972	71,447	73,990	76,599	79,276
Proportion treated by any treatment*	91.17%	91.17%	91.17%	91.17%	91.17%
- in case of positive guidance for mild patients	62,883	65,139	67,457	69,836	72,277
Proportion treated by any treatment [3]	78.11%	78.11%	78.11%	78.11%	78.11%
- with current guidance for mild patients	49,115	50,877	52,688	54,546	56,452
Proportion of all treated on AChEIs or memantine [3]	92.72%	92.72%	92.72%	92.72%	92.72%
Mild AD patients being treated					
- in case of positive guidance for mild patients	58,306	60,399	62,548	64,754	67,017
- with current guidance for mild patients	45,540	47,175	48,853	50,576	52,344
Donepezil Market Share for Mild AD patients [3]	63.37%	63.37%	63.37%	63.37%	63.37%
Mild AD patients being treated with donepezil					
- in case of positive guidance for mild patients	36,950	38,276	39,638	41,036	42,470
- with current guidance for mild patients	28,860	29,896	30,959	32,051	33,171
Increase in patients per year being treated with donepezil	8,090	8,380	8,679	8,985	9,299

Note: * Assume to go up to level of moderate patients, see below. Source: 1. NAO 2007. 2. Assumption based on 68% overall referral rate for mild and moderate patients. 3. McLeod 2009.

Table 20 provides the estimated number of moderate patients eligible for treatment. The number would remain the same if NICE extended its recommendation to mild patients as AChEIs are already recommended for moderate Alzheimer patients. It is estimated that 29,583 moderate patients will be on donepezil treatment in 2011 and 31,877 moderate patients in 2015.

Table 20. Patients with Moderate AD on Treatment

	2011	2012	2013	2014	2015
Proportion of diagnosed AD patients with moderate disease [1]	32.10%	32.10%	32.10%	32.10%	32.10%
	66,607	67,866	69,147	70,449	71,772
Proportion of diagnosed moderate AD patients referred to specialists [2]	85%	85%	85%	85%	85%
	56,616	57,686	58,775	59,882	61,007
Moderate AD patients on treatment [3]	91.17%	91.17%	91.17%	91.17%	91.17%
	51,617	52,593	53,586	54,595	55,620
Proportion of treated patients treated on AChEIs or memantine [3]	92.69%	92.69%	92.69%	92.69%	92.69%
	47,843	48,747	49,668	50,603	51,553
Donepezil Market share for moderate AD patients [3]	61.83%	61.83%	61.83%	61.83%	61.83%
Moderate AD patients being treated with donepezil	29,583	30,142	30,711	31,290	31,877

Note: * A small proportion of patients are treated by neuroleptics. **There is no change expected in the market for moderate disease.
Source: 1. NAO 2007. 2. Assumption based on 68% overall referral rate for mild and moderate patients. 3. McLeod 2009.

The donepezil drug budget taking into account both branded and generic donepezil is presented in Table 21. With a NICE guidance recommending donepezil for the treatment of patients with mild AD, the AD drug cost to the NHS in England and Wales in 2011 is estimated to be £71.0 million decreasing to £60.1 million in 2015. Compared with the estimates based on the current guidance, a recommendation for donepezil in mild AD patients results in a 9% increase in AD drug costs in 2011 and a budget impact of £5.7 million. The budget impact of AD drugs resulting from the changed recommendation for donepezil is projected to be £4.9m in 2012, £5.5m in 2013, £6.1m in 2014, and £6.8m in 2015.

Table 21. Drug Costs Budget Impact

	2011	2012	2013	2014	2015
Donepezil costs with current guidance for mild AD patients	£65,368,055	£50,419,077	£51,370,935	£52,338,198	£53,321,296
Donepezil costs with positive guidance for mild AD patients	£71,020,596	£55,285,979	£56,846,328	£58,443,024	£60,077,015
Budget impact	£5,652,540	£4,866,902	£5,475,393	£6,104,826	£6,755,719

Costs of direct health care associated with donepezil are included in Table 22. The cost of care incurred in a home care setting is estimated to increase as more patients are being kept out of expensive institutionalised care. The drop in the institutional care costs due to a higher proportion of patients being treated is estimated to be almost £10 million per year. The total budget impact including both drug and non-drug costs/savings is estimated to be net savings of £1.6m in 2011, £3.4m in 2012, £3.8m in 2013, £4.3m in 2014 and £4.7m in 2015.

Table 22. Costs of Care and Total Budget Impact (in thousands)

	2011	2012	2013	2014	2015
Direct costs in home care setting with current guidance for Mild AD patients	£475,674	£489,361	£503,383	£517,735	£532,425
Direct costs in home care setting with positive guidance for Mild AD patients	£476,511	£490,313	£504,454	£518,929	£533,746
Home Care Costs Budget Impact	*£837*	*£952*	*£1,071*	*£1,194*	*£1,321*
Direct costs in institutional care setting with current guidance for Mild AD patients	£496,906	£510,957	£525,348	£540,075	£555,144
Direct costs in institutional care setting with positive guidance for Mild AD patients	£488,794	£501,730	£514,968	£528,500	£542,336
Institutional Care Costs Budget Impact	*-£8,113*	*-£9,227*	*-£10,381*	*-£11,574*	*-£12,808*
Drugs Budget Impact	*£5,653*	*£4,867*	*£5,475*	*£6,105*	*£6,756*
Total Budget Impact (including drugs cost)	*-£1,623*	*-£3,409*	*-£3,835*	*-£4,276*	*-£4,732*

4.3 Sensitivity Analysis

The sensitivity of the above results was explored by testing some of the parameters that are estimated with uncertainty. The results of the sensitivity analysis can be found in Tables 23-26. As the key parameter that is likely to change as a consequence of a revised NICE recommendation for mild AD patients, this was tested by initially altering treatment rates. An increase in treatment rates to 95% affects the AD drugs cost budget by imposing 29% higher drug costs in 2011 and 21% higher drug costs in 2015, with an estimated budget impact of £7.3million in 2011 and £8.2 million in 2015.

Different diagnosis rates have been cited by recent literature, with the most recent report quoting 33% (NAO 2010). While for people aged 80 years or older the NAO 2007 report estimated a 49.2% diagnosis rate. Therefore the diagnosis rate was varied by plus 10% and minus 14% to cover the variation in literature estimates. An increase in diagnosis rates by 10% affects the AD drugs cost budget by imposing 21% higher drug costs than those estimated, with an estimated budget impact of £6.8million in 2011 and £8.2 million in 2015. A 14% decrease in diagnosis rates affects the drugs budget impact a percentage decrease of 30%, with an estimated budget impact of £3.9 million in 2011 and £4.8 m in 2015.

A 10% increase in referral rates (from base case rate of 68%) increases the drugs budget impact to £6.6 million in 2011 and £7.5 million in 2015. The equivalent decrease in referral rates provides a drugs budget impact of £4.7 million in 2011 and £5.9 million in 2015. The percentage change in the drugs budget impact is equivalent to 17% in 2011 and 11% in 2015.

If discontinuation is changed from 0% to 20% (a compliance rate of 80%) annually the drugs budget impact decreases by 11% to £5.0 million in 2011 and £6.0 million in 2015. The drug budget impact with no drop in generic price results in an increased budget impact from 2012, by about 32%. If annual increase in referral rate was 2% instead of 1% the drugs budget impact would increase by 10% in 2012 and 32% in 2015.

Table 23. Sensitivity Analysis – Impact of Parameter Changes on Donepezil Drug Budget

Year	2011	2012	2013	2014	2015
Base Case	*£5,652,540*	*£4,866,902*	*£5,475,393*	*£6,104,826*	*£6,755,719*
10% Increase in diagnosis rates	£6,848,000	£5,896,206	£6,633,387	£7,395,939	£8,184,491
14% Decrease in diagnosis rates	£3,979,728	£3,426,591	£3,855,005	£4,298,164	£4,756,432
4% Increase in treatment rates	£7,308,959	£6,165,808	£6,820,517	£7,497,381	£8,196,951
4% Decrease in treatment rates	£3,995,109	£3,567,200	£4,129,446	£4,711,418	£5,313,605
10% Increase in referral rates	£6,594,631	£5,593,546	£6,215,755	£6,859,128	£7,524,190
10% Decrease in referral rates	£4,710,450	£4,140,258	£4,735,031	£5,350,523	£5,987,248
1% Increase in Referral increase rat	£5,652,540	£5,373,939	£6,508,612	£7,683,835	£8,900,611
80% Compliance rate	£5,054,078	£4,351,618	£4,895,686	£5,458,477	£6,040,457
No price reduction in donepezil	£5,652,540	£6,429,196	£7,233,016	£8,064,499	£8,924,332

Table 24 and Table 25 below highlight the budget impact of parameter changes on the home care budget impact and the institutionalisation budget impact respectively. An increase in the proportion of patients treated increases the home care budget impact, however decreases the institutionalisation budget impact. Thus decreasing the proportion of patients treated decreases the home care budget impact and increases the institutionalisation budget impact. When the proportion of patients with diagnosis, or referred and compliant are increased, there is greater number of patients on treatment leading to changes in similar directions as described for treatment rate. A decrease in these parameters has the opposite effect.

Table 24. Sensitivity Analysis – Impact of Parameter Changes on Home Care Budget

Year	2011	2012	2013	2014	2015
Base Case	*£836,669*	*£951,627*	*£1,070,606*	*£1,193,679*	*£1,320,949*
10% Increase in diagnosis rates	£1,013,617	£1,152,888	£1,297,029	£1,446,131	£1,600,317
14% Decrease in diagnosis rates	£589,065	£670,003	£753,771	£840,422	£930,027
4% Increase in treatment rates	£1,081,847	£1,205,603	£1,333,619	£1,465,966	£1,602,753
4% Decrease in treatment rates	£591,342	£697,496	£807,432	£921,226	£1,038,972
10% Increase in referral rates	£976,114	£1,093,708	£1,215,369	£1,341,168	£1,471,208
10% Decrease in referral rates	£697,225	£809,546	£925,843	£1,046,190	£1,170,689
1% Increase in Referral increase rate	£836,669	£1,050,769	£1,272,632	£1,502,424	£1,740,340
80% Compliance rate	£748,087	£850,874	£957,256	£1,067,298	£1,181,093
No price reduction in donepezil	£836,669	£951,627	£1,070,606	£1,193,679	£1,320,949

Table 25. Sensitivity Analysis – Impact of Parameter Changes on Institutionalisation Budget (in thousands)

Year	2011	2012	2013	2014	2015
Base Case	*-£8,113*	*-£9,227*	*-£10,381*	*-£11,574*	*-£12,808*
10% Increase in diagnosis rates	-£9,828	-£11,179	-£12,576	-£14,022	-£15,517
14% Decrease in diagnosis rates	-£5,712	-£6,496	-£7,309	-£8,149	-£9,018
4% Increase in treatment rates	-£10,490	-£11,690	-£12,931	-£14,214	-£15,541
4% Decrease in treatment rates	-£5,734	-£6,763	-£7,829	-£8,932	-£10,074
10% Increase in referral rates	-£9,465	-£10,605	-£11,784	-£13,004	-£14,265
10% Decrease in referral rates	-£6,760	-£7,850	-£8,977	-£10,144	-£11,351
1% Increase in Referral increase rate	-£8,113	-£10,188	-£12,340	-£14,568	-£16,875
80% Compliance rate	-£7,254	-£8,250	-£9,282	-£10,349	-£11,452
No price reduction in donepezil	-£8,113	-£9,227	-£10,381	-£11,574	-£12,808

Table 26 highlights the budget impact of parameter changes on the overall NHS budget impact, including both drug costs and cost offsets. An increase in treatment rates by 4% provides an estimated total budget impact of £2.1 million savings in 2011 and £5.7 million savings in 2015.

The equivalent decrease in treatment rates provide an estimated budget impact of £1.1 million savings in 2011 and £3.7 million savings in 2015. An increase in diagnosis rates by 10% provides an estimated budget impact of £1.9 million savings in 2011 and £5.7 million savings in 2015. A 14% decrease in diagnosis rates results in estimated savings in the total budget impact of £1.1 million in 2011 and £3.3 m in 2015. If a compliance rate of 80% was applied annually the budget impact would be affected by a reduction of 11% to £1.4 million savings in 2011 and £4.2 million savings in 2015. In the unlikely event of a generic price level equalling current list price, would still on aggregate lead to net savings, although 45% less compared to the base case, of about £1.6 million in 2011 and £2.6 million in 2015.

Table 26. Sensitivity Analysis – Impact of Parameter Changes on Total Budget

Year	2011	2012	2013	2014	2015
Base Case	*-£1,623,306*	*-£3,408,643*	*-£3,834,813*	*-£4,275,650*	*-£4,731,518*
10% Increase in diagnosis rates	-£1,966,621	-£4,129,539	-£4,645,840	-£5,179,910	-£5,732,190
14% Decrease in diagnosis rates	-£1,142,905	-£2,399,889	-£2,699,938	-£3,010,314	-£3,331,272
4% Increase in treatment rates	-£2,099,000	-£4,318,361	-£4,776,900	-£5,250,957	-£5,740,917
4% Decrease in treatment rates	-£1,147,322	-£2,498,368	-£2,892,149	-£3,299,746	-£3,721,501
10% Increase in referral rates	-£1,893,857	-£3,917,564	-£4,353,342	-£4,803,943	-£5,269,734
10% Decrease in referral rates	-£1,352,755	-£2,899,721	-£3,316,284	-£3,747,357	-£4,193,302
1% Increase in Referral increase rate	-£1,623,306	-£3,763,757	-£4,558,451	-£5,381,545	-£6,233,741
80% Compliance rate	-£1,451,439	-£3,047,753	-£3,428,802	-£3,822,966	-£4,230,568
No price reduction in donepezil	-£1,623,306	-£1,846,348	-£2,077,190	-£2,315,977	-£2,562,905

Sensitivity analyses of key parameters indicate that the potential drug cost implications to the NHS in England and Wales vary between £3.9m and £7.3 million in 2011. The drug cost impact in 2015 is estimated to range between £4.8m and £8.9 million. Please note that the largest drop in price is assumed to be 30% whereas in reality the reduction could be much larger. The total budget impact is expected to vary between £1.1 and £2.1 million in savings in 2011 and between £2.6 million savings and £6.2 million savings in 2015. The budget impact is sensitive to treatment and diagnosis rates, plus generic price levels after 2012, while referral rates and compliance rates had a slight impact.

4.4 Discussion

The budget impact of a guidance recommending donepezil in the treatment for mild AD patients would be consistent with findings regarding cost-effectiveness of donepezil among mild AD patients. At the same time the analysis shows that even under conservative assumptions, the impact of such a recommendation on the drug budget would be small relative to treatment costs of AD. Furthermore, taking into account cost offsets, a positive recommendation is estimated to result in cost-savings in the health systems overall. Seen another way, if the NICE guidance remains as a recommendation for donepezil in moderate AD patients only, then this will cost the NHS in England and Wales an additional £1.6 to £4.7 million between 2011 and 2015.

Recommending donepezil for mild AD patients in addition to moderate AD patients is estimated to result in overall savings to the NHS in England and Wales for a number of reasons. Considering current service capacity limitations, only minor increase is expected in referrals by GPs to specialists in the short run. At the same time, for historical reasons a considerable number of mild and moderate AD patients among the referred *are* already treated by donepezil. According to patient level data from Dementia Trak covering 2009 (McLeod 2009), three quarters with mild, and almost 90% of patients with moderate disease who present in specialist clinics are being treated with AChEIs or memantine. A small percentage of patients are taking neuroleptics, and only 8% in moderate and 21% in mild disease patients presenting to memory clinics remain untreated. Among those treated with AChEIs, between 50 and 60% are already taking donepezil.

There are a number of limitations of the budget impact model. First, the model structure is simple, not taking into account mortality or treatment duration, and assumes a steadily increasing flow of patients each year. While it may result in inaccuracies, the assumptions are likely lead to overestimated budget impact. Some key parameters are estimated with large uncertainty, particularly the rate of diagnosis and the referral rates to specialists and the *changes* in referral and treatment rates due to a change in NICE guidance. These parameters influence the total budget estimated for any year, and subsequently the incremental budget impact of a positive recommendation. The estimated total drug budget for donepezil is similar to company projections providing some validity to our estimates. These parameters are based on best estimates given current services and based on moderate disease experience. Apart from choosing the more conservative values (i.e. higher proportions), quite wide range of plausible values have been tested in sensitivity analyses to address these limitations.

The budget impact estimates are derived by applying conservative assumptions including no change in Aricept price and only a 30% reduction in the price of generic donepezil after February 2012. A higher price reduction will mean a much larger saving to the NHS.

In conclusion, under conservative assumptions a recommendation by NICE would increase the drug budget by about £5.7 million in 2011, and ranging from £4.9 and £6.8 million thereafter. If cost-offsets in terms of falling institutionalization rates are considered, the overall budget impact for the NHS and personal social services would actually amount to net savings of £1.6 million in 2011 and ranging from £3.4 to £4.7 thereafter.

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