NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Shire	Shire supports the recommendations of the draft ACD for the treatment of Alzheimer's disease (AD) with the AChEI drugs, namely that both mild and moderate AD patients be treated on the NHS, consistent with the licensed indications. We believe that this sound guidance is well supported by the clinical and cost effectiveness data collected over the last 20 years. In particular we note that the appraisal committee has recognised that AChEI treatment results in a delay in time to institutionalisation.	Comment noted.
Shire	We have only one comment to make on the content of the draft guidance. In paragraph 3.4, the drug regimen for galantamine mentions only the older twice daily treatment (tablets), which is now used only to a minor extent. The once daily (capsule) treatment now predominates and its omission from 3.4 is serious. Therefore the once daily regimen must be emphasised in paragraph 3.4. We suggest the following amended wording: 3.4 Galantamine (Reminyl, Shire) is an AChE inhibitor, which works by increasing the concentration of acetylcholine at sites of neurotransmission and also modulates activity at nicotinic receptors. Galantamine has a marketing authorisation in the UK for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type. The formulation most frequently prescribed is the once daily capsules (Reminyl XL), given initially at 8 mg once daily for 4 weeks and then increased to 16 mg once daily for at least 4 weeks. Maintenance treatment is 16-24 mg once daily depending on assessment of clinical benefit and tolerability.	Comment noted. Section 3.4 of the FAD has been amended to include the cost and dosing regimen of galantamine once daily.
Shire	Regarding the specific questions which you pose, our answers are as follows: • Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion	Comments noted.

Consultee	Comment	Response
	or belief? No	
Novartis	Novartis welcomes the new draft recommendation for the use of the three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine within their licensed indications for mild to moderate Alzheimer's disease. In addition, we strongly agree with the point to "take into account adverse event profile, expectations around adherence, medical comorbidity, possibility of drug interactions and dosing profiles."(Section 1.1) However, Novartis would like to raise three points which we feel need to be addressed in the final advice: • Further discussion of drug interactions is warranted • Incorrect drug acquisition costs are quoted in the ACD • Misleading description of the 9.5 cm2 rivastigmine patch as a 'lower dose patch'	Comment noted. Individual responses to each of the three points are addressed below.
Novartis	Detailed comments from Novartis on the ACD (Oct 2010) 1. Further discussion of drug interaction is warranted In Section 1.1 it raises the point that drug interactions should be considered when selecting the optimum therapy. Novartis believes that this important point warrants further discussion. We suggest a brief discussion is included within Section 4.3.4 to 4.3.10 Clinical effectiveness donepezil, rivastigmine and galantamine. Novartis suggests this discussion should include a summary of the differences in the metabolism of the three AChE inhibitors, for example: "Major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Furthermore, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances. Donepezil is metabolised by the cytochrome P450 system. Isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil.2 Drug interaction studies have shown that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce	Comment noted. NICE appraises the clinical and cost effectiveness of technologies. A full analysis of drug interactions, unless it refers specifically to the clinical and cost effectiveness estimates of the technologies in question, is outside the scope of this appraisal. Therefore, we have referred readers of the guidance to the individual Summaries of Product Characteristics for each of the technologies which provides a full description of all relevant drug interactions.

Consultee	Comment	Response
	the levels of donepezil.2 Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Galantamine is partially metabolised by various cytochromes, mainly CYP2D6 and CYP3A4. Therefore, during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine, or fluoxetine) or CYP3A4 (e.g. ketoconazole or ritonavir) patients may experience an increased incidence of cholinergic adverse reactions, predominantly nausea and vomiting." For a succinct summary of drug interactions Novartis would like to draw your attention to the 10th edition of the Maudsley Guidelines page 393.	
Novartis	2. Incorrect drug costs In Section 4.2.16 "Assessment Group's model mild to moderate Alzheimer's disease" it highlights the monthly drug costs of memantine and rivastigmine capsules. Novartis are surprised that the monthly drug cost of rivastigmine capsules is quoted as £98. In the TAR it explains that the reference for the drug costs is BNF 58 to derive the Sept 2009 costs. In BNF 58 it is very clear that the cost of a rivastigmine capsule is £1.19 per capsule. This is the same for all doses and all pack sizes. This gives a monthly cost of £72.30 and not £98. Novartis suggests that reference to rivastigmine capsule costing £98 per month is corrected in the final advice since it is currently factually incorrect. Novartis would also like to point out that this mistake was also raised at the TAR stage. Table 113 in the current TAR still contains this factual inaccuracy. In addition, Novartis notes that the monthly cost of memantine is included in this section. Memantine is not licensed for use in a mild Alzheimer's disease population so Novartis suggests that the discussion of memantine is removed from this section too. Novartis believes that the aim of this paragraph is to give the maximum and minimum drug acquisition costs for treating mild to moderate Alzheimer's disease. According to Table 113 in the TAR the maximum drug acquisition cost is for 10mg once daily donepezil (Aricept) which is quoted as costing £97 per month, and the lowest is for rivastigmine patches (10cm2) which are quoted as costing £79 per month. Novartis suggests that Section 4.2.16 is updated to state: "The monthly drug costs	Comment noted. The monthly cost of £72 was included in the revised cost effectiveness analyses from the Assessment Group following consultation on the Assessment report. The monthly cost of rivastigmine has been amended in section 4.2.16 of the Final Appraisal Determination.

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	were based on the BNF edition 58 and ranged from £79 for rivastigmine patches to £97 for donepezil."	
Novartis	3. Misleading description of the 9.5 cm2 rivastigmine patch as a 'lower dose patch' In Section 4.1.28 it refers to the 9.5mg/day rivastigmine patch as the lower dose transdermal patch. Novartis would like to highlight that in the BNF it lists two rivastigmine transdermal patches: 4.6 mg/day and 9.5 mg/day. Novartis believes that many readers will understand the 4.6 mg/day to be the 'lower dose' patch because it is the lowest dose patch available in the UK. Novartis therefore suggests to avoid confusion to the reader that the 9.5 mg/day patch is not referred to as a 'lower dose patch' in the guidance because this is the highest licensed dose in the UK. Novartis suggest that section 4.1.28 is changed to: "The 9.5 mg/day transdermal patch produced fewer side effects than the capsule (12 mg/day)." **References** Exelon® (rivastigmine) Summary of Product Characteristics. April 2010. Aricept ® (donepezil) Summary of Product Characteristics. May 2009. Reminyl ® (Galantamine) Summary of Product Characteristics. March 2010. Taylor D et al. (2009) The Maudsley Prescribing Guideline, 10th Revised edition. Infoma Healthcare.	Comment noted. This has been amended in section 4.1.28 of the Final Appraisal Determination.
Pfizer/Eisai	Eisai and Pfizer are pleased to have the opportunity to comment on the Appraisal Consultation Document (ACD) and welcome the draft recommendations for donepezil for patients with both mild and moderate Alzheimer's disease (AD). Alzheimer's disease is a serious progressive neurodegenerative disorder with devastating consequences for the patient. Donepezil has a significant body of clinical evidence, previously accepted by NICE and restated in the Eisai/Pfizer submission, 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	Comment noted.

Consultee	Comment	Response
	therapy results in a rapid loss of these benefits.	
Pfizer/Eisai	Both the PenTAG and Eisai/Pfizer economic models have shown consistent results in demonstrating that donepezil delays progression of symptoms and institutionalisation and so is cheaper and more effective than best supportive care in both mild and moderate AD patients. Donepezil is not only cost effective but delivers savings to the NHS in a particularly cost constrained environment. Indeed, a recommendation in mild disease for donepezil is likely to increase expenditure on cholinesterase inhibitors in England and Wales but this is outweighed by savings resulting from the effect of donepezil in delaying institutionalised care costs (£8.1 million in 2011 rising to £12.8 million in 2015). 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. These economic benefits are likely to be even more pronounced once generic versions of the cholinesterase inhibitors are available in 2012.	Comment noted.
Pfizer/Eisai	The draft guidance from NICE is long overdue and ensures that AD patients receive the only licensed pharmacological treatments available to treat the symptoms of AD. This draft recommendation encourages active therapeutic management from the earlier symptomatic stages of disease and will be a major element in achieving the aims of the National Dementia Strategy. These recommendations also support the dementia Quality Standards and should be referred to as a stand alone Statement to ensure implementation.	Comment noted.
Pfizer/Eisai	• Has all of the relevant evidence been taken into account? Eisai and Pfizer would like to highlight two pieces of evidence where further comment is required. Donepezil is the only cholinesterase inhibitor to have data from a large 12 month placebo controlled trial and there is very little mention of the availability of this long term high quality data in the ACD. The Winblad (Winblad et al. 2001) and Mohs randomised controlled trials (Mohs et al. 2001) show statistically significant differences favouring donepezil in cognition, functional and behavioural symptoms compared with placebo in mild to moderate AD patients. Some recognition of the availability of these 12 month data is warranted in the ACD as no other cholinesterase inhibitor has similar long term placebo-controlled trial data.	Comment noted. Section 4.1.11 of the Final Appraisal Determination has been amended to acknowledge the 12 month data available.
Pfizer/Eisai	In the technologies section, the description of donepezil in section 3.3 contains incorrect price information. The current NHS list price for a pack of 28 5mg tablets	Comment noted. Section 3.3 of the Final Appraisal Determination has been

Consultee	Comment	Response
	is £59.85 and £83.89 for a pack of 28 10mg tablets. These prices were updated in BNF version 60 (see http://bnf.org/bnf/bnf/60/61149.htm?q=donepezil&t=search&ss=text&p=3#_61149).	amended to reflect the BNF 60. However costs in other sections reflect those used in the individual economic models.
Pfizer/Eisai	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Where clinical and cost effectiveness evidence has been summarised in the ACD, Eisai and Pfizer are content that reasonable interpretations are made. However, in section 4.1.30 of the ACD, the Bullock trial is considered the only head to head study of sufficient quality to be reported (Bullock et al. 2005). This two-year prospective, multicentre, double blind, parallel-group randomized controlled trial 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 and was powered to detect a difference in efficacy between both compounds. However, what was not mentioned in the ACD is that this study failed to meet its primary endpoint. Moreover, there is no mention of the statistically significant higher rates of some adverse events and discontinuations in the rivastigmine compared with the donepezil treatment arms (Birks et al., 2006) which may result in an overestimation of the benefit of rivastigmine in the LOCF intent to treat (ITT) analysis. In addition, 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. A more balanced interpretation of this trial is required in the ACD.	Comment noted. Further information on the Bullock study has been added to the Final Appraisal Determination to provide more details of the data.
Pfizer/Eisai	• Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Eisai and Pfizer welcome the recommendations for cholinesterase inhibitors for mild and moderate AD patients in line with their licences. In particular we welcome the acknowledgement that donepezil is both clinically and cost effective. There is a wealth of both clinical and cost effectiveness evidence to support this recommendation for donepezil. The findings of the systematic review Eisai and Pfizer undertook for this review of	Comment noted.

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	TA111 match those from the PenTAG review. Most of the donepezil trials assessed the impact on cognition, whereas the measurement against functional and behavioural trials was less prevalent. There have also been a multitude of meta-analyses and independent systematic reviews of donepezil evidence (Campbell et al. 2008*, Birks et al. 2006, Hansen et al. 2008). These reviews have agreed that donepezil has favourably impacted on these efficacy domains, in particular, on cognition, functional status and behavioural symptoms. Further randomized and non-randomised evidence demonstrates donepezil results in improvements in neuropsychiatric symptoms which are accompanied by a reduction in levels of caregiver stress and burden. Non-randomised study designs were not assessed by PenTAG but an open-label extension study (Burns et al. 2007) and a prospective observational study (Wallin et al. 2007) show that after three years donepezil was associated with a positive effect on global and cognition outcomes in patients with mild and moderate AD. Open label data also shows that donepezil is associated with significant delays (an average of 17.5 months) in the time to institutionalisation (Geldmacher et al. 2003). New cost effectiveness evidence submitted by Eisai and Pfizer for this review of TA111 is consistent with that generated independently by PenTAG, even though both models have approached the same research question in different ways. Both assessments show that donepezil is cheaper and more effective, and so dominates best supportive care in both mild and moderate AD patients. This consistency in the cost effectiveness evidence for donepezil should reassure the NHS that donepezil represents value for money. Indeed, expanding the symptomatic treatment to both mild and moderate AD patients should result in cost-savings as the additional drug costs are outweighed by the large estimated savings in institutionalisation costs. This draft guidance is also consistent with the National Dementia Strategy (Department of Health 2009), which was published in February 2009, and aims to ensure that significant improvements are made to dementia services across three key areas: earlier diagnosis and intervention, higher quality of care, living well with dementia in care homes, and reduced use of anti-psychotic medication. Increased	

* Some studies included severe AD patient populations (out of licence for donepezil)

Consultee	Comment	Response
	use of cholinesterase inhibitors may help contribute to each of these objectives. In addition, more money is spent on anti-psychotic drugs for AD patients (£128 million) in the UK than on the four anti-dementia drugs (£100 million). A reduction in the inappropriate use of anti-psychotic medication will also help fund the increase in cholinesterase inhibitor prescribing.	
Pfizer/Eisai	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None. **References provided, but not reproduced here.**	Comment noted.
Lundbeck	Lundbeck is pleased to submit its response to the NICE Appraisal Consultation Document (ACD) on the multiple technology appraisal (MTA) of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (AD) (review of NICE technology appraisal guidance 111). Lundbeck would like to express their appreciation to the NICE Appraisal Committee and the Peninsula Technology Assessment Group (PenTAG) for their comprehensive review of the data for memantine. In particular, Lundbeck would like to thank the Committee for the consideration of their feedback on the technology assessment report (TAR) developed by PenTAG. We believe that the revision of several elements of the PenTAG assessment, particularly in relation to the economic model, in response to the comments from Lundbeck and other stakeholders, has ensured that the evaluation of the evidence for memantine is now improved in terms of robustness and validity. Lundbeck feel that the NICE MTA for AD treatments has been a transparent process that has ensured that all AD patients in England and Wales, including those in the most advanced and severe stages of the disease, will now get access to clinically effective medications that represent the most efficient use of NHS resources. The Lundbeck response to the NICE ACD has three main components. Firstly, while Lundbeck recognise that much of their feedback on the TAR was considered	Comment noted. Individual responses to each of the three points are addressed below.

Consultee	Comment	Response
	and implemented we feel it is important to highlight several aspects that relate to the differences in approach between the Lundbeck review of the data and the PenTAG approach, which gave rise to conflicting conclusions on the efficacy of memantine as an adjunct treatment to acetylcholinesterase inhibitors (AChEIs). Secondly, feedback is also provided on the approach to the use of individual patient data, with the aim of starting a dialogue that will facilitate the use of such data in future appraisals. Finally, comments and suggested amendments on specific aspects of the ACD are provided.	
Lundbeck	**1 Differences between the Lundbeck and PenTAG Approach** This section will consider the differences in approach to both the clinical evaluation of memantine and to the economic evaluation. **1.1 Clinical Evaluation** There are several differences between the Lundbeck and PenTAG conclusions on the efficacy of memantine in the treatment of AD. These conflicting results can be explained by an examination of the approach taken by Lundbeck and PenTAG to the evaluation of the clinical data. Lundbeck believe that it would be useful to elaborate on these differences in the ACD in order to improve the clarity for readers. This is described in more detail below. The main clinical evidence package for memantine consists of 6 six-month randomised placebo-controlled trials: Three in patients with moderately severe to severe AD, including two with memantine monotherapy (FRX-MD-011, MRZ-96052) and one with memantine as an adjunct to donepezil (FRX-MD-023) Three in patients with mild to moderate AD including two with memantine monotherapy (Lu-996794, FRX-MD-105) and one with memantine as an adjunct to AChEIs (FRX-MD-126) It is important to first highlight the major difference in the way the clinical data for memantine in the treatment of AD was considered. The Lundbeck synthesis of the evidence pooled data from all six trials but, in line with the memantine licence, excluded mild patients from trials that included mild-	Comment noted. Sections 4.1.32, 4.1.38, 4.1.39 and 4.1.40 of the Final Appraisal Determination have been amended to explain the differences between the Lundbeck and PenTAG submissions and conclusions.

Consultee	Comment	Response
	moderate AD. This meta-analysis of the data has been published in a peer reviewed journal. The mixed patient population in the Lundbeck analysis was composed of: • Moderate AD patients withdrawn from AChEIs; • Moderate patients contraindicated for AChEIs; • Moderate patients requiring adjunct treatment while on stable dose with AChEIs; and • Patients with severe AD. The key conclusions of this published meta-analysis, as highlighted in the Lundbeck submission, were: "A statistically significant treatment effect in favour of memantine was found with respect to all four key efficacy domains. Memantine was found to be effective in attenuating deterioration of cognition, function, behaviour and global status (Table 3.1) and no evidence of heterogeneity was found for the data analysed. This analysis was published by Winblad et al., 2007" An investigation of potential differences in the memantine efficacy according to the included patients' profiles (severity, presence of background AChEI treatment and history of past AChEI treatment) revealed no heterogeneity in the memantine efficacy across the different groups and the pooling of data across these populations is therefore appropriate. In particular, the efficacy of memantine versus placebo as adjunct treatment or monotherapy, and the interaction between treatment effect and presence or absence of background treatment was assessed and found to be non significant. This is clearly stated in the appendix of the Lundbeck submission for memantine: "Memantine was significantly superior to placebo on most outcomes, both as adjunct therapy and monotherapy. Other outcomes, namely disability in adjunct (p=0.0551 in OC and p=0.0600 in LOCF) and global health state in adjunct for the LOCF analysis (p=0.0666), were close to significance level, despite lower sample size compared with base case analyses. The interaction between treatment effect and presence of background treatment was not significant."	
Lundbeck	In contrast to the approach taken by Lundbeck, PenTAG considered the clinical	Comment noted.

Consultee	Comment	Response
	efficacy of memantine in two separate groups: • A monotherapy analysis including only the two trials in moderately severe to severe AD (FRX-MD-01, MRZ-9605). This did not include the monotherapy trials in mild-moderate patients (Lu-99679, FRX-MD-10) as data in the moderate population only were not included in the primary publications of these trials. However, it should be noted that the data in the moderate patient sub group was available in published meta-analyses. • An adjunct analysis including the clinical trial in moderately severe to severe patients (FRX-MD-02) and in mild moderate patients (FRX-MD-12). It is important to note that in their analysis PenTAG included all patients from trial FRX-MD-12 despite some patients having mild AD and therefore being outside the current licensed indication for memantine. The reasons for PenTAG choosing to synthesise the data as described above are unclear. It would have been possible for PenTAG to exclude the mild patients from trial FRX-MD-12 and there appears to be no justification for why this approach was adopted.	In the Assessment Report, the reasons for evaluating monotherapy and adjunct therapy separately are given on page 144, section 4.6.4.1.

Consultee	Comment	Response
	In the ACD the following PenTAG conclusions on the efficacy of memantine as an adjunct treatment to AChEIs are described: NICE statement, ACD 4.1.40 p26: "The Assessment Group found one new trial that compared memantine plus a stable dose AChE inhibitor with an AChE inhibitor plus placebo. This trial did not show any benefit from combining memantine with an AChE inhibitor on cognitive, functional, behavioural or global outcomes. A trial that compared memantine plus donepezil with donepezil plus placebo was included in NICE technology appraisal guidance 111. Pooling the new trial with the previous trial of memantine in combination with an AChE inhibitor did not show any additional benefit from combination therapy." NICE statement, ACD 4.3.14 p52: "The Committee noted evidence that showed no statistically significant benefit for combination treatment with memantine and AChE inhibitors for cognitive, functional, behavioural or global outcomes." The discrepancy between the PenTAG and Lundbeck conclusions on the efficacy of memantine as an adjunct treatment to AChEIs can be explained by the different approaches. While PenTAG included all patients from study FRX-MD-12 in their meta-analysis (including mild patients who fall outside memantine indication), Lundbeck included only moderate patients from this study. In the ACD the lack of significant benefit in study FRX-MD-12 is highlighted although no reference is made to the significant efficacy that was reported in FRX-MD-02 across all the domains; cognition, functional disability, behaviour and global. This omission is particularly important as study FRX-MD-02 is the only trial for adjunctive use of memantine that includes exclusively patients within the licensed indication for memantine.	Comment noted. In the Assessment Report, the inclusion criteria for the systematic review are explained on page 63, section 4.1.2.2.

Consultee	Comment	Response
Lundbeck	The differences between the included studies are described in the ACD, but they are stated only very briefly and this does not provide sufficient information: NICE statement, ACD 4.1.43 p27: "The Assessment Group concluded that the evidence in the three manufacturer's submissions was broadly consistent with its own, but highlighted that there were differences between the studies included by the manufacturers and its own review." In order to enhance the transparency of the recommendations for readers, it is proposed that the results from the Lundbeck pooled analysis of all patients, in line with the memantine licence, should be described in more detail, and the differences between this analysis and the PenTAG approach in regards to the adjunct memantine analysis is highlighted.	Comment noted. In the Assessment Report, the inclusion criteria for the systematic review are explained on page 63, section 4.1.2.2.

Consultee	Comment	Response
Lundbeck	Lundbeck proposes that the following statements should be included in the ACD: • Study FRX-MD-02 conducted in moderately severe to severe AD (thereby completely within the memantine indication) concluded that there was a significant benefit from combination treatment with memantine plus donepezil compared to donepezil alone on all four domains of AD symptoms: cognition, functional disability, behaviour and global. • Although study FRX-MD-12 showed no significant benefit with memantine in the total population of mild to moderate patients the differences in the baseline severity of the patients from FRX-MD-02 and FRX-MD-12 are a possible reason for the differences in clinical outcomes. • When the data was pooled and the mild patients, who are not within the memantine indication, were excluded a significant benefit of memantine as an adjunct to AChEIs was reported.	Comment noted. In the Assessment Report, the inclusion criteria for the systematic review are explained on page 63, section 4.1.2.2.
Lundbeck	**1.2 Economic Evaluation** It is important to note that the Lundbeck and PenTAG conclusions on the cost-effectiveness of memantine were consistent overall despite some differences in modelling approach. In terms of the cost-effectiveness evaluation, the difference in the approaches taken by Lundbeck and PenTAG to the clinical evaluation also explains the variation in the choice of data sources for the economic model. With the Lundbeck economic evaluation the LASER-AD cohort was used to develop the cost-effectiveness model. This observational study is most representative of current management of AD patients in the UK, and within this study patients could be treated with or without AChEIs. In contrast the PenTAG economic model utilised an observational cohort (the Wolstenholme study) in which patients received no AD treatments.	Comment noted. The Final Appraisal Determination describes the modelling approaches of Lundbeck and PenTAG in sections 4.2.24 to 4.2.34.
Lundbeck	**2 Access to Individual Patient Data**	Comment noted.

Consultee	Comment	Response
	As stated during the Appraisal Committee meeting held on the 25th of August, Lundbeck is not opposed to the submission of individual patient data (IPD) from clinical trials to NICE if this is deemed necessary in order to improve the evaluation process. It should be noted that PenTAG did not request any IPD from Lundbeck to assist them in their evaluation of the efficacy of memantine. Lundbeck feel there are several important practical issues that should be highlighted in regard to the submission of IPD: • Memantine is licensed by Lundbeck but also by partner companies and therefore authorisation from these partners would be required before Lundbeck could release data to NICE or to PenTAG; • All partners contributed to the clinical trial development of memantine and different standard database formats were used across the memantine trials. The PenTAG analysts would therefore require training on all utilised database formats; • All analyses of IPD from clinical trials performed by PenTAG should be assessed by the manufacturers, who are familiar with the datasets, to ensure quality of the programming and of the analyses. The practical issues highlighted above are relevant not only for the appraisal of memantine but also for many other therapies being developed by Lundbeck. Due to the current size of Lundbeck, the vast majority of products in development are being co-developed with partner companies and therefore the first two issues described above are of particular importance. In order to ensure that any future technology appraisals are conducted in the most robust and transparent way possible, Lundbeck would be very pleased to discuss the development of a process for the sharing of IPD with NICE and the analysis of this data by the independent academic group.	
Lundbeck	**Specific Comments** The following section offers specific comments on the ACD with the proposed amendments by Lundbeck. **3.1 Data on Observational Studies** The observational data for donepezil is comprehensively included in the ACD as	Comment noted. Amendments have been made in the Final Appraisal Determination section 4.1.38.

Consultee	Comment	Response
	supporting the clinical benefit of this therapy, as follows: NICE statement, ACD 4.1.11 p16: "The manufacturer of donepezil included prospective longitudinal and observational studies to support the view that cognitive benefits from donepezil are maintained for up to 3 years. The manufacturer also presented evidence from randomised and nonrandomised controlled trials to demonstrate that benefit was lost when treatment was stopped, the benefits of continuing treatment despite initial decline or stabilisation of MMSE, and the impact of improvement of neuropsychiatric symptoms on caregiver stress and burden." For memantine there are a number of observational studies that provide data to support the controlled trial data, and in the ACD the following is included for memantine: NICE statement, ACD 4.1.32 p23: "Evidence from observational studies was also presented." Although NICE mention the observational studies submitted by Lundbeck for memantine a summary of the findings from this data was not integrated in the ACD. In order to ensure the consistent presentation of observational data across the AD treatments considered in the technology appraisal Lundbeck suggest the inclusion of the following paragraph within the ACD: "The manufacturer of memantine included prospective longitudinal and observational studies which support the view that the cognitive and functional benefits of memantine are maintained for years (Atri et al., 20088), that memantine delays time to institutionalisation (Lopez et al.,20099), that memantine initiation reduces the trend in increasing antipsychotic drug use among AD patients (Vidal et al., 200810), that memantine treatment reduces the need for antipsychotic medication (Martinez et al., 200811) and that memantine discontinuation is associated with an increased utilisation of antipsychotics compared to continuous memantine treatment (Fillit et al., 2008a12 and 2008b13)."	
Lundbeck	**3.2 Safety of Memantine** NICE statement, ACD 4.3.15 p53: "The Committee considered the evidence of adverse effects associated with memantine and noted that some patients	Comment noted.

Consultee	Comment	Response
	experience agitation that resolves when the drug is stopped." In the TAR, this statement was based on one study only. Lundbeck believes that this conclusion is unfair and does not reflect the full evidence available for memantine, which actually shows fewer agitation adverse events in memantine treated patients compared to placebo treated patients. This reduction of agitation adverse events is consistent with the efficacy of memantine on the symptom of agitation that is acknowledged by NICE in the current ACD. The relevant extract from the Lundbeck response to the TAR is provided below: "In the TAR data on the safety for memantine as a monotherapy is reported based on one study only MEM-MD-12 (in which patients are treated with stable dose of AChEIs) and reports that "the main AEs in the memantine group were agitation and hypertension" (section 4.6.4.3.6; page 153). It should be noted that the incidence of agitation was lower in memantine treated patients than placebo treated patients. In the case of safety it is more appropriate to synthesise data across multiple trials. A meta-analysis on the tolerability and safety data from clinical trials published in 200814 would be a more appropriate source of safety data. Other reviews of safety data from all memantine clinical trials are also available. This analysis reports that the most common adverse events with memantine are agitation and falls and both have numerically lower incidence than placebo." We would therefore propose that the wording in the ACD should be rewritten to read as follows: "The Committee considered the evidence of adverse effects associated with memantine. The main AEs in the memantine group were agitation and hypertension, but the incidence of agitation was lower in memantine-treated patients than-placebo treated patients."	Amendments have been made in the Final Appraisal Determination section 4.1.39.
Lundbeck	**3.3 Inclusion of Additional Details on the Meta-Analysis** As described previously, the approach to the evaluation of the clinical data by Lundbeck and PenTAG differed, with the differences in the trials included in the meta-analyses conducted by both groups. The meta-analysis reported by Lundbeck is included in the ACD as described below:	Comment noted. Amendments have been made in the Final Appraisal Determination sections 4.1.33 to 4.1.36.

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	NICE statement, ACD 4.1.33 p24: "Studies included in the manufacturer's meta-analysis for memantine reported a statistically significant benefit in ADAS-cog or SIB compared with placebo at the end of study or at 24 weeks." NICE statement, ACD 4.1.34 p24: "The manufacturer's meta-analysis for memantine in moderate to severe disease showed a statistically significant difference compared with placebo on the ADCS-ADL19 and ADCS-ADL23." NICE statement, ACD 4.1.35 p24: "The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant (p = 0.03) benefit in terms of NPI and NPI-Nursing Home version." NICE statement, ACD 4.1.36 p25: "The standard mean difference in the manufacturer's meta-analysis for memantine in moderate to severe disease for global outcomes (CIBIC-plus) compared with placebo was statistically significant." In the ACD the conclusions from the PenTAG analysis are supported by the accompanying data, as shown in the example below: NICE statement, ACD 4.1.33 p23-24: **"**When data from this trial were added to those of NICE technology appraisal guidance 111, a statistically significant benefit was reported at 12 weeks, but this was not maintained at 24-48 weeks (mean changes from baseline versus placebo of 4.147 [p = 0.025] and 3.254 [p = 0.245] at 12 and 24/28 Weeks using SIB score)." We suggest that adding figures from the Lundbeck analysis in the text will increase the transparency for the reader. The following suggestions are recommended: NICE statement, ACD 4.1.33 p24 "Studies included in the manufacturer's meta-analysis for memantine reported a statistically significant benefit in ADAS-cog or SIB compared with placebo at the end of study or at 24 weeks **(SMD = -0.26, p < 0.0001)**." NICE statement, ACD 4.1.34 p24: "The manufacturer's meta-analysis for memantine in moderate to severe disease showed a statistically significant difference compared with placebo on the ADCS-ADL19 and ADCS-ADL23 **(SMD =**	

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	-0.18, p = 0.007)." NICE statement, ACD 4.1.35 p24: "The results of the meta-analysis by the manufacturer of memantine in moderate to severe disease showed a statistically significant (**SMD = -0.12,** p = 0.03) benefit in terms of NPI and NPI-Nursing Home version." NICE statement, ACD 4.1.36 p25: "The standard mean difference in the manufacturer's meta-analysis for memantine in moderate to severe disease for global outcomes (CIBIC-plus) compared with placebo was statistically significant **(SMD = -0.22, p < 0.0001)**."	
Lundbeck	**3.4 Miscellaneous Comments and Suggested Amendments** The following text amendments are suggested to correct inaccuracies and provide additional clarification for the reader. 1 NICE statement, ACD 4.1.24 p20: **"**These used the Progressive Deterioration Scale (PDS) and ADCL-ADL as outcome measures.**"** In this sentence, "ADCL-ADL" should be changed to "ADCS-ADL".	Comment noted. Amendments have been made in the Final Appraisal Determination section 4.1.24.
Lundbeck	2 NICE statement, ACD 4.2.25 p40: "The manufacturer submitted a Markov cohort model of the cost effectiveness of memantine compared with best supportive care over a 5-year time horizon in people with moderate to severe Alzheimer's disease and a subgroup of people with aggression, agitation and/or psychotic symptoms at baseline **based on the NPI scale (≥ 3)**." To improve the transparency of the subgroup definition, the bold text should be changed to "based on the NPI scale (at least one domain among agitation/aggression, delusion and hallucination with a score ≥ 3)"	Comment noted Amendments have been made in the Final Appraisal Determination section 4.2.25.
Lundbeck	3 NICE statement, ACD 4.2.28 p41: "The subgroup that was analysed had not previously been accepted by the Appraisal Committee for NICE technology appraisal guidance 111." Lundbeck acknowledges that a subgroup analysis in behaviourally disturbed patients was previously submitted to NICE for technology appraisal guidance 111 and was not accepted by the Appraisal Committee. However, the subgroup analysis presented here represents patients with APS (agitation/aggression and/or psychosis), and is different to that previously submitted. This APS subgroup is	Comment noted The Committee considered the information provided in the manufacturer submission for memantine for this appraisal, including the subgroup as defined. The Committee noted that a

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	defined based on the grounds of clinical expertise (please see appendix B of the Lundbeck submission "Consensus Statement on APS Sub-group Definition").	subgroup had also been considered by the Committee in TA111. However, the Committee did not review the subgroup evidence from TA111. For clarity, amendments have been made in the Final Appraisal Determination section 4.2.28.
Lundbeck	4 NICE statement, ACD 4.2.28 p42: "In addition, because the trials used observed cases with last observation carried forward in the analysis instead of an intention-to-treat analysis, the Assessment Group was concerned that the clinical-effectiveness estimates may have been biased." As stated in the Lundbeck response to the TAR: "studies use the same criteria to define the population analysed (All randomised patients who took at least one dose of investigational medicinal product (memantine or placebo) and had at least one valid post-baseline assessment on primary endpoint)". Therefore, all analyses have been performed on intent-to-treat population using the observed cases approach, with a last observation carried forward analysis also included to confirm the results. Lundbeck request that the statement is removed.	Comment noted Amendments have been made in the Final Appraisal Determination section 4.2.28.
Lundbeck	5 NICE statement, ACD 4.2.33 p44: "The manufacturer's model also assumed a higher cost of, and a shorter time in, pre-institutional care with treatment (1.73 years in the manufacturer's model compared with 1.5 years in the Assessment Group's model)." This conclusion seems erroneous as a longer time in the pre-FTC state is observed in the Lundbeck model (1.73 years) compared to the time in pre-institutionalisation in PenTAG model (1.5 years). "Shorter time" should be changed to "longer time".	Comment noted Amendments have been made in the Final Appraisal Determination section 4.2.33.
Lundbeck	6 NICE statement, ACD 4.3.13 p52: "This evidence reported a statistically significant benefit of memantine for cognitive outcomes and neuropsychiatric inventory score on agitation, aggression and/or psychotic symptoms in this subgroup." NICE statement, ACD 4.3.35 p63: "The Committee also heard from clinical specialists and the manufacturer that memantine appears to have cognitive and behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms, which are more common in people with severe Alzheimer's	Comment noted Amendments have been made in the Final Appraisal Determination sections 4.3.13 and 4.3.35.

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	disease." In order to more accurately reflect all the findings from the analyses of memantine efficacy in the subgroup, these paragraphs should be changed as follows: NICE statement, ACD 4.3.13 p52: "This evidence reported a statistically significant benefit of memantine for cognitive**, functional and global** outcomes and neuropsychiatric inventory score on agitation, aggression and/or psychotic symptoms in this subgroup." NICE statement, ACD 4.3.35 p63: "The Committee also heard from clinical specialists and the manufacturer that memantine appears to have cognitive**, functional and global** and behavioural effects, particularly in people with aggression, agitation and/or psychotic symptoms, which are more common in people with severe Alzheimer's disease."	
Lundbeck	7 NICE statement, ACD 4.2.28 p42: "There was also a lack of clarity about the categorisation of 'dependence', inclusion of data from patients with mild disease, poor reporting of statistical analyses and lack of validation from an external source." NICE statement, ACD 4.2.28 p42: "Benefits to carers were not included in the model, and mapping of health-related quality-of-life data to EQ-5D was poorly described." Lundbeck believes these statements on their economic model are inappropriate and unfairly represent the evidence submitted. All these issues have been addressed in the answer to the TAR submitted by Lundbeck on the 4th August 2010. In their response, Lundbeck acknowledged the lack of validation of the predictive equation against an external source and clarified all other issues. Lundbeck would like to highlight that detailed information on each of these points were highlighted both in the memantine dossier and in the Lundbeck response to the TAR and to reiterate that all information required to support their response can be provided upon request. Lundbeck would welcome constructive feedback on how to improve the reporting of such analyses, both in the context of this evaluation and also to enable improved reporting in future appraisals. **References provided but not reproduced here.**	Comment noted Comments on the Assessment Report were circulated to and considered by the Committee. The Assessment Group responded to particular comments on their report. Therefore, amendments have been made in the Final Appraisal Determination section 4.2.28.

Consultee	Comment	Response
Lundbeck	Lundbeck would like to express their appreciation to the NICE Appraisal Committee and PenTAG for the opportunity to review the executable copy of the economic model developed by PenTAG. As described in the Lundbeck response to the Appraisal Consultation Document, we feel that the NICE review of AD treatments has been a transparent process that has ensured that patients in England and Wales will now get access to clinically effective medications that represent the most efficient use of NHS resources. Lundbeck has undertaken a comprehensive review of the updated economic model and find it to be greatly improved in regard to both technical and face validity compared to the original evaluation. The cost-effectiveness estimates for memantine in the new model have improved in terms of robustness and validity. However, in the absence of a full technical report it is difficult to properly assess the relevance of some of the changes implemented in this revised model. Although many of Lundbeck's comments on the original economic evaluation have been addressed some of the technical issues and model errors highlighted in our response to the technology assessment report (submitted in August 2010) remain. However, it is not anticipated that these issues and inaccuracies will have a substantial effect on the conclusions of the economic model and therefore Lundbeck have not detailed them further here.	Comment noted.
British Geriatrics Society	We welcome the Appraisal Consultation document as a balanced and thorough summary of the current evidence and would strongly support the Committee's preliminary recommendations. These provide practical guidance to promote clinical and cost effective use of the drugs. The emphasis on decisions being based on holistic assessment of severity and response, rather than bound by a score on one particular measure, reflects good clinical practice and will help to ensure equality of access to treatment for all who will benefit.	Comment noted.
British Geriatrics Society	Minor changes/corrections to the document that the Committee might consider are: Page 3, 1.1, 2nd para (and Page 4, 1.2, 3rd para): "Only specialists in the care of patients with dementia (that is old age psychiatrists and those specialising in learning disability…")	Comment noted. The original wording has been retained in section 1.1 of the Final Appraisal Determination as the wording allows for this group of specialists.

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	Page 6, 2.3: The recent paper in the BMJ (Rait et al. BMJ 2010; 341: c3584) provides recent UK data on survival. This showed that median survival of people in primary care aged 60-69 years at dementia diagnosis was 6.7 (interquartile range 3.1-10.8) years, falling to 1.9 (0.7-3.6) years in those aged 90 years and over.	Additional information has been added to section 2.3 to emphasise that survival may be affected by age.
British Geriatrics Society	Minor changes/corrections to the document that the Committee might consider are: Page 9, 3.4: Galantamine is now given once daily as prolonged release capsules, so should now read "It is given initially at 8mg prolonged release capsule once daily for 4 weeks and then increased to 16mg once daily for at least 4 weeks. Maintenance treatment is 16-24mg once daily depending on …." Page 9, 3.7: Need to add "Alternatively rivastigmine transdermal patches are available, initially using a 4.6mg patch/day, that may be increased to a 9.5mg patch/day for at least 4 weeks"	Comment noted. Section 3.4 has been updated with information about galantamine prolonged release formulation. Section 3.7 has been amended to clarify the available dose of rivastigmine patches.
British Geriatric Society	Page 10, 3.10: Delete unnecessary sentence "In 2005, the license was extended to include moderate disease" Page 11, 4.1.1: "the British Geriatrics Society" Page 21, 4.1.28: "The highest dose (9.5mg/day) transdermal patch produced fewer side effects than the highest dose capsule (12mg/day)" Page 62, 4.3.34: "the impact of memantine on behavioural..."	Comments noted. Section 3.10 of the Final Appraisal Determination has been amended to delete this sentence. Section 4.1.1 now reads 'British Geriatrics Society' As above, 4.1.28 has been amended to clarify the available doses of rivastigmine patches. Section 4.3.34 has been amended.
Alzheimer's Society	Alzheimer's Society welcomes the opportunity to comment on the Appraisal Consultation Document (ACD). We strongly support the recommendations contained in the ACD and recommend that they are upheld in the Final Appraisal	Comment noted.

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	Determination. This would represent an important step forward in the development of an effective and comprehensive package of care for people with Alzheimer's disease. It would also support the achievement of the important public policy aim of improving rates of diagnosis and early intervention for people with dementia. Alzheimer's Society believes there are a number of ways in which the economic modelling could be improved (as discussed below) and these are also likely to improve the cost effectiveness profile of the treatments. We have the following comments to make:	
Alzheimer's Society	**1. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Alzheimer's Society believes the recommendations within the ACD are a suitable basis for guidance to the NHS. The review of published evidence carried out to inform this review has confirmed previous systematic review findings[1, 2] that all four of these drug treatments are clinically effective. The ACD also acknowledges that, for a significant proportion of people with Alzheimer's disease, the drugs have benefits that are not likely to be picked up by the standard scales used within clinical trials (para 4.3.7). This conclusion is consistent with the reports of carers and people with dementia that the drug treatments have benefits for many and are an important addition to a comprehensive package of care. In addition, the review has confirmed that these drugs are cost-effective. Both the manufacturers' and Assessment Group models found the drug treatments to be cost effective, enabling NICE to be particularly confident that the drug treatments represent an effective use of NHS resources. In addition, with regard to memantine, the ACD notes that 'The Committee therefore concluded that the cost effectiveness of memantine may have been underestimated in the Assessment Group's model for patients with severe Alzheimer's disease, although by how much is uncertain.'	Comment noted.

1. Alzheimer's (review of TA111) table of comments on ACD to PM for publication

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Alzheimer's Society	***Anticholinesterase drug treatments*** We are very supportive of the recommendation to extend prescription of the anticholinesterase drug treatments to people with an MMSE above 20. As we explained in our submission to this review, people with Alzheimer's disease feel very strongly that the goal of anticholinesterase treatment should be the extension of the period during which symptoms are most mild. This is when people are best able to cope with symptoms and retain some independence and quality of life. This is the stage at which a delay in progression is most wanted. Provision of potentially effective drug treatment in the mild stages of Alzheimer's disease also supports the important policy aims of increasing rates of diagnosis and early intervention. We know that individuals experiencing symptoms often delay seeking help and also that GPs can be reluctant to diagnose dementia because they believe there is little that can be done. The availability of a drug treatment in the early stages is likely to encourage people to seek help from their GPs. It also provides an additional incentive to GPs to diagnose people and refer them to specialist services.	Comment noted.
Alzheimer's Society	**Memantine** Alzheimer's Society is also extremely supportive of the recommendation that memantine should be available as a treatment option to people in the moderate and severe stages of Alzheimer's disease. Memantine is the only licensed and effective drug treatment for people in the severe stages of dementia As stated in the ACD, published evidence demonstrates that memantine is clinically effective. This is supported by reports to the Alzheimer's Society from people with dementia and carers. Although sometimes it is more difficult to understand the experience of people in the later stages of Alzheimer's, we now know more about the importance of trying to maintain quality of life throughout the course of dementia. Many people have reported to us that prescription of memantine has resulted in important and meaningful benefits, for example being able to use the toilet unaided. The improvements that memantine can bring to behavioural symptoms are	Comment noted.

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	particularly important, as these are the symptoms that can be most distressing to people with dementia and their carers.[3] We discuss under section 2 the consideration given to behavioural symptoms by the Appraisal Committee. The reliance on anti-psychotic drugs as a treatment for behavioural symptoms highlights the importance of having a clinically and cost effective treatment, that has none of the serious side effects of antipsychotic drugs, available on the NHS. The reduction of antipsychotic prescription by two-thirds by November 2011 is a clearly stated public policy aim and this NICE recommendation will provide helpful support to achieving this aim.	
Alzheimer's Society	**2. Has all of the relevant evidence been taken into account? Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** We support the conclusion that the four drugs are clinically and cost effective. We also believe that the current Assessment Group model improves upon the SHTAC model in important ways. We particularly welcome the acknowledgement that there is heterogeneity of costs and quality of life in the pre-full time care state. However, there are still a number of acknowledged limitations and we feel it would be important to work together to achieve an improved consensus model for future appraisals. It is disappointing that, as the ACD acknowledges, 'important gaps in the evidence remain'. Some of these gaps will pertain to further improvements of the model as suggested above. For example, the evaluation still fails to acknowledge the benefits the drugs can provide to carers. We recognise that there is limited data on this and that carer benefit was included in a sensitivity analysis. However, given the significant burden on carers of people with dementia and the increased risk of psychological morbidity and reduced quality of life,[4] we believe it is important to develop methods for incorporating any benefits to carers. We still believe that in the absence of any good data on carer quality of life, methods should be developed to incorporate the findings from clinical trials that the drug treatments can reduce the time carers spend caring.	Comment noted. These comments were presented to the Committee as the second meeting and the comments were acknowledged but it was decided not to amend the wording of the guidance document. The document already includes recommendations for further research.

Consultee	Comment	Response
	It is also disappointing that there are no data from clinical trials on quality of life for carers and for people with Alzheimer's disease, and also with regard to service use. We recognise that it is unlikely these issues will be addressed for currently licensed drugs as they will soon be going off patent and there will be limited further trials. We do however agree it would be extremely important to make recommendations that trials for new emerging treatments do address these issues. However, there are other sources of evidence addressing quality of life. We welcome the Appraisal Committee's recognition of patient evidence of the benefits of treatment. As noted, these benefits may not be captured in scales normally used within clinical trials but can be very meaningful in the context of people's day-to-day lives (para 4.3.7.). It is important to use the personal accounts of individual experience with the drug treatments alongside data from clinical trials to develop a better understanding of their benefits. Because of the lack of up to date evidence on patterns of service usage, the Assessment Group has had to rely on out of date and limited data from the Wolstenholme study. We believe that using more up to date evidence would result in the drug treatments appearing more cost-effective as the differential between costs in the early and severe stages would be greater – in 2010 people do not receive services until their needs are greater and individuals entering institutions have a higher level of need. As acknowledged in para 4.2.23 the failure to assume a treatment benefit in behavioural and psychological symptoms is a limitation of the model. This is particularly a problem for memantine. Amelioration of these symptoms is one of the most important benefits of the drug and we note the Committee's conclusion in para 4.3.13 that 'on the basis of the manufacturer's evidence and clinical specialist testimony that memantine appears to have an effect on these symptoms.' As noted in our submission, we would like to see work carried out to develop a model that uses available data to capture the contribution of MMSE score, NPI score (including key symptoms such as agitation/aggression, psychosis, depression and apathy) and functional ability to quality of life and costs. It is particularly important to incorporate behavioural symptoms into a model because of the evidence of their	

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	impact on costs.[5] Alzheimer's Society would also like to see risperidone used as a comparator for the treatment of behavioural symptoms. Risperidone is licensed for the "short-term treatment (up to six weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others". Although the response to behavioural and psychological symptoms should be individualised and based on good person centred care the reality is that antipsychotics are widely used as the first-line treatment.	
Alzheimer's Society	**Additional comments** The Audit Support Guidance for TA111 makes it clear that 100% of people with moderate Alzheimer's should be considered for treatment with one of the anticholinesterase drugs. We would welcome a similar audit standard to be established for the revised guidance. This would be an important driver to encourage local areas to increase rates of diagnosis of Alzheimer's disease, which remain unacceptably low.[6] In light of the well-recognised problems in recognising and responding appropriately to symptoms of Alzheimer's disease we would welcome the opportunity to work with NICE on communicating the revised guidance to GPs and other healthcare professionals, should the ACD remain unchanged. We believe the recommendations as they stand would act as an incentive to GPs to refer people to memory assessment services for diagnosis and access to a range of support, including potential treatment with one of the four licensed drugs. The value to people with dementia of having access to an effective memory assessment service that offers a comprehensive service is recognised within the NICE Quality Standards. The recommendations within the ACD would help to support the achievement of these standards. References	Comment noted. NICE issues clinical audit documents for all of its published guidance. NICE has an implementation team that works with GPs and other healthcare professionals to communicate revisions to guidance.

Consultee	Comment	Response
	1 Birks J (2006) Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews.* Issue 1. 2 McShane R, Areosa Sastre A, Minakaran N (2006) Memantine for dementia. *Cochrane Database of Systematic Reviews*. Issue 1. 3 Deimling GT and Bass DM (1986) Symptoms of mental impairment among elderly adults and their effects on family caregivers. *Journal of Gerontology.* 41:778-84. 4 Moise P, Schwarzinger M, Um M-Y (2004) *Dementia Care in 9 OECD Countries: A Comparative Analysis.* Paris: DELSA/ELSA/WD/HEA. 5 Murman DL, Chen Q, Powell MC, et al (2002) The incremental direct costs associated with behavioural symptoms in Alzheimer's disease. *Neurology.* 59: 1721-9. 6 National Audit Office (2007) *Improving Services and Support for People with Dementia.* NAO	
Royal College of Nursing	The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111) Nurses caring for patients with Alzheimer's disease reviewed the documents on behalf of the RCN. Appraisal Consultation Document – RCN Response The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below: i) Has the relevant evidence has been taken into account? The evidence considered seems comprehensive. ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?	Comment noted. The wording in 1.3 of the Final Appraisal Determination was discussed by the Committee has been changed to 'benefit in cognition, functioning 'or' behaviour'. NICE considers equality issues throughout the scoping and development of its guidance and will issue an equality impact assessment with the Final Appraisal Determination.

Consultee	Comment	Response
	The summaries of the clinical and cost effectiveness on the use of this health technology seem appropriate. iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? The Royal College of Nursing welcomes the recommendations of the Appraisal Committee on the use of these drugs for the treatment of Alzheimer's disease. It is welcome that people in earlier stages of the disease are now being offered treatment. This decision would be a huge relief for patients and carers of people with Alzheimer's disease for whom early access to these treatments have helped reduce the devastating effect this disease can have on them. We would, however like to suggest a minor change to recommendation 1.1 (bullet 3rd point) which we believe could have bigger implications for clinical practice. We felt that the clause 'and' should be replaced by 'or' in respect of the guidance for continuation of treatment after monitoring response. The current sentence reads that there should be benefit in cognition, functioning and behaviour. We considered that this should be amended to reflect that any symptomatic relief in any of the domains is an important factor and can have a profound effect in improving quality of life for people with dementia and their family and carers. iv) Are there any equality related issues that need special consideration that are not covered in the ACD? We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. Guidance on the use of this technology should also be mindful of the impact it may have on reducing socio-economic inequalities.	
Royal College of Psychiatrists	Thank you for sending this document for comments. The Faculty of Old Age Psychiatry very much welcomes the proposed change in guidance to now allow	Comment noted. The Committee discussed the wording of

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	use of all three cholinesterase inhibitors and memantine within their licensed indication. As you will know, we previously fundamentally disagreed with the previous NICE Guidance limiting these drugs, and the economic analysis on which this was based, and are now pleased to see that the drugs are felt to be highly cost effective. This change will significantly improve the management of Alzheimer's disease within the UK, and bring us more into line with clinical practice in other countries. I would suggest the following modifications be considered by the committee. 1. The recommendation remains for six monthly monitoring, yet there is no evidence base for this. In practice, these drugs are usually continued for two to three years and routine monitoring every six months serves no useful purpose. There is a real danger that, because of increased prescribing and limited NHS resource in the years ahead, a large proportion of resource will be taken up with unnecessary routine monitoring of patients who are otherwise well. We would suggest that the recommendation is changed to "patients who continue on the drugs should be reviewed according to both clinical need and local shared care arrangements". It is noteworthy that there is now a requirement for primary care to undertake reviews of people with dementia and their carers every 15 months. 2. Given that all drugs are now deemed cost effective, then there should be no recommendation that treatment should normally be started with the drug with the lowest acquisition cost. This varies considerably both in geographical location and over time, and will undoubtedly alter again when the drugs come off patent in 2012. There are important differences in drug interactions and side effects between the different agents, as well as in mode of administration and these clinical factors should be the driving force in choice of agent rather than lowest acquisition cost. It is not unusual for the drug with the lowest acquisition cost to be rivastigmine, which is associated with much higher costs in terms of more frequent monitoring (for dose titration) and also is often associated with more frequent gastrointestinal side effects. 3. There is reference made on many occasions to the lack of evidence for combined benefit of the cholinesterase inhibitor with memantine. At stages of more	section 1.3 of the Final Appraisal Determination and have changed the wording of the six month review to 'regularly'. The wording of section 1.4 states that, where appropriate, clinical factors may dictate the choice of AChE inhibitor. NICE publishes recommendations based on the clinical and cost effectiveness of technologies. It is not within the scope of this appraisal to determine how recommended technologies are prescribed. Prescribers should refer to the Summary of Product Characteristics for prescribing information. Specific reference to the MMSE has been removed from the recommendations in section 1.1. However, much of the evidence of clinical effectiveness includes the MMSE as a measure of cognition. Therefore, it is still referred to in the evidence section and considerations. The economic model produced by the Assessment Group made the assumption that being in an institution was equivalent to severe disease. Therefore, this issue is discussed in the evidence section. However, this is not

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	moderate to severe dementia it may well be appropriate for memantine to be introduced and the two can be safely co-prescribed. It might then be appropriate for the cholinesterase inhibitor to be withdrawn, but there may well be a necessary period where a cholinesterase inhibitor is co-prescribed with memantine, though comment could be made that this should not be routinely continued in the longer term. 4. There remains a heavy reliance on use of the MMSE to judge dementia severity which is not appropriate. The severity scores are given as if there is some determined truth behind these cut-offs; they are very arbitrary and staging of dementia relies far more on a holistic process which takes into account a patient's functionality, activities of daily living, and neuropsychiatric features, as well as the MMSE score, based on factors including their premorbid education level, extent of concurrent problems such as dysphasia or hearing and visual impairment. We would strongly recommend that the MMSE is not used as a means for determining eligibility for cholinesterase inhibitors; it is quite sufficient to state that the drugs should be used within their licensed indication. 5. It is also important to note that moving to a residential home or institutionalisation should not necessarily indicate that the stage of severe dementia has been reached and that cholinesterase inhibitors should be withdrawn. There are many factors influencing institutionalisation, neuropsychiatric features and carer stress being two of the most powerful. Neither of these would indicate the need for withdrawal of cholinesterase inhibitors; indeed, if this were the case, then neuropsychiatric features might well worsen.	mentioned in the recommendations section 1.1 to 1.6 of the Final Appraisal Determination and it is not intended that in clinical practice, severity is equated to living in an institution.
Association of British Neurologists	*We believe that the analysis and review has been done carefully *The only potential patient grouped disadvantaged might be the patient with a high educational background who may be significantly impaired compared with premorbid function but scores above 26 on the MMSE	Comment noted. Those with a high educational attainment have been recognised in the guidance.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical expert 1	In my view the committee have examined the available evidence and have adapted their findings to take account of the most recent updates of their cost effectiveness model. Input has been received from a wide variety of consultees and reflects a broad spectrum of opinion, knowledge, expertise and experience from a number of sources. The clinical effectiveness of these drugs has not been a source of major dispute for several years and effects are generally acknowledged to be modest. However the effects of almost every well researched intervention for dementia is also modest and there is a huge variety in the standard of supportive care across the UK. Should NICE choose to confirm their recommendations, as detailed in the consultation document, my belief is that this would represent a major boost to services who are trying to implement the National Dementia Strategies. Wider availability of these drugs will have the effect of attracting more people with dementia into contact with services with much more appropriate care planning as a consequence. Earlier intervention will reduce the degree of adverse change in the relationship between a person with dementia, their carers, family and social networks. This will allow other recommendations of the strategy to be implemented. I am aware that commissioners may react badly to the suggestion that more money should be spent on medication in this time of financial crisis. However it is well established that the costs of severe dementia greatly exceed the per capita costs of mild or moderate form of the disease. Anything which helps stabilise a patient in the earlier stages will be of ultimate benefit. I suspect that many professionals will be concerned that commissioners will use the guidance to spend less money on supportive care and yet it is the careful integration of interventions, each of which might have modest benefit, which ultimately leads to the best outcome for an individual. Commissioners should be reassured by the fact that generic versions of cholinesterase inhibitors will be available within 18 months which should keep costs down.	Comment noted.
Clinical expert 1	1.1 In the main the provisional recommendations are appropriate though some alterations are suggested below. I believe that NICE have taken the correct step	Comment noted.

Nominating organisation	Comment	Response
	in recommending that cholinesterase inhibitors and Memantine are used within their UK licence indications. In clinical practice the cholinesterase inhibitors all seem to have equal effects and it appears reasonable to treat these as a class rather than look for individual differences.	
Clinical expert 1	Continuing to include the statement about initiation by specialists is likely to be controversial amongst primary care colleagues. However dementia strategies recommend comprehensive and competent specialist assessment and I believe this continues to be appropriate. The key is in getting the patient into specialist services at as early a stage as possible to allow comprehensive multidisciplinary and multi-agency care planning to take place.	Comment noted. The recommendations in section 1.4 of the Final Appraisal Determination allow for local shared care arrangements.
Clinical expert 1	By contrast there are significant disadvantages in continuing to insist on 6 monthly assessments. The danger here is that formal clinic appointments become clogged up with relatively routine reviews. This can impair the ability of services to see new patients. This might become more difficult still if the number of people on cholinesterase inhibitors and Memantine continues to grow. From experience there is little doubt that many patients become acutely distressed at the realisation that they are performing more poorly on intellectual tests, whereas relatives become concerned that drugs might be removed and tend to under-report the degree of problems they are experiencing day-to-day. Although general practitioners are now paid to review patients on a Primary Care Dementia Register every 15 months there is no service specification for the nature of that review. NICE may consider either making review of cholinesterase inhibitors and Memantine part of the specification for GP review or alternatively recommend that patients taking these drugs should be in contact with a specialist Older Peoples Mental Health Team rather than fixing timescales for review.	Comment noted. The Committee discussed the wording of section 1.3 of the Final Appraisal Determination and have changed the wording of the six month review to ‘regularly’.

Nominating organisation	Comment	Response
Clinical expert 1	I wonder if it is still reasonable to consider acquisition cost as the primary driver if other issues such as environmental costs are taken into account. In reality there is very little difference between the cost of initiating each of the drugs as the number of clinic appointments, length of assessment, utilisation of neuro-imaging and access to multidisciplinary care are all broadly similar for each patient but costs will vary significantly from provider to provider. The committee has accepted that an alternative cholinesterase inhibitor could be prescribed under certain circumstances but I wonder if there is any real benefit from keeping the recommendation about acquisition costs.	Comment noted. The wording of section 1.4 states that, where appropriate, clinical factors may dictate the choice of AChE inhibitor.
Clinical expert 1	1.2 The document makes several references to the lack of evidence for additional benefit from the combination of a cholinesterase inhibitor plus Memantine by comparison with either drug used as monotherapy, but there is no specific recommendation about using the combination or about how changeover of the two drugs should be accomplished. In reality it would be very difficult to justify the discontinuation of a cholinesterase inhibitor in someone who had previously been a good responder and then commence a drug of which the prescriber might have little experience. Almost inevitably there is going to be some overlap and this should be acknowledged. It may be necessary to state that a period of a cholinesterase inhibitor being co-prescribed with Memantine will be necessary in any cases where changeover of drugs is being considered. More information should come from the results of the DOMINO-AD Study though even this may not give a definitive answer.	NICE publishes recommendations based on the clinical and cost effectiveness of technologies. Prescribers should refer to the Summary of Product Characteristics for prescribing information. Reference has been made to the DOMINO-AD study.
Clinical expert 1	1.3 While it is obviously appropriate to mention Learning Disability there was a view in some quarters that TA111 discriminated against people who were cognitively normal prior to developing dementia despite evidence for efficacy being very much more robust in that group than in those with learning disability who develop dementia. The reason for this was that drugs could be prescribed to people with learning disability on the basis of clinical assessment, yet people who were cognitively normal had to have a particular value in a relatively narrow range on a single scale. I am pleased to see that this has been removed from the consultation document.	Comment noted. Specific reference to the MMSE has been excluded from the recommendations in section 1.1 to 1.6 of the Final Appraisal Determination. The guidance also now makes reference to those with high educational attainment.

Nominating organisation	Comment	Response
Clinical expert 1	1.4 It is never appropriate to use a cognition score alone for assessing the severity of dementia. Dementia is a multi-faceted illness including functional and behavioural domains as well as carer interactions. All of these need to be considered when determining severity of dementia whether or not a patient is being treated with medication. Healthcare professionals, particularly those less experienced in the use of assessment scales, such as GPs, should be aware of the inter-rater variability of scoring on basic scales such as the MMSE. As with blood pressure major changes in a patient's regime should not be undertaken on the strength of a single assessment. This is particularly important when considering criteria for withdrawing the drugs. As an example, I provide training sessions on the use of the MMSE and a 7-9 point range in scoring amongst people watching the same interview is not exceptional.	Specific reference to the MMSE has been removed from the recommendations in section 1.1 to 1.6 of the Final Appraisal Determination. However, much of the evidence of clinical effectiveness includes the MMSE as a measure of cognition. Therefore, it is still referred to in the evidence section and considerations.
Clinical expert 1	In the economic models institutionalisation is taken as equivalent to severe Alzheimer's disease. I recognise that duration of treatment has the greatest impact on the cost effectiveness model but it would be important to be explicit about not equating institutionalisation with severe dementia in clinical practice. People with dementia enter institutional care for a number of reasons and many people, particularly those who live alone, tend to enter full time care at an MMSE score considerably in excess of 10. It would be important that medication was not routinely discontinued in this population. Indeed this may be construed as direct discrimination i.e. a person was being restricted access to effective treatment on the grounds of where they resided.	The economic model produced by the Assessment Group made the assumption that being in an institution was equivalent to severe disease. Therefore, this issue is discussed in the evidence section. However, this is not mentioned in the recommendations section 1.1 to 1.6 and it is not intended that in clinical practice, severity is equated to living in an institution.

Comments received from commentators

None received

Comments received from members of the public

Role	Section	Comment	Response
NHS Professional	Section 1	Patients should be able to choose which specialist team manages their dementia and monitors their medication. Current arrangements of red listing drugs and block contracts with local services curtail patient choice. The patchy uptake of shared care arrangement with GPs hinder patient access to treatment as local arrangements may offer a poor service and delay to treatment. This is a form of post-code prescribing.	Comment noted. The recommendations in section 1.4 of the Final Appraisal Determination allow for shared care arrangements.
NHS Professional	Section 2	Does not give upper limit to MMSE for Mild AD	Comment noted. The recommendations in section 1 of the Final Appraisal Determination no longer refer to specific MMSE scores
NHS Professional	Section 5	Please see above comments for maintaining patient choice. Patients should be able to choose the service that manages their dementia and initiates and monitors their medication. Current arrangements of funding of dementia medication (e.g. block contracts with single providers) limit patient choice and disparity of service across geographical areas.	Comment noted. The recommendations in section 1 of the Final Appraisal Determination allow for local shared care arrangements.
NHS Professional	Section 1	The assertion at 4.3.44 that monitoring needs to be done six monthly and by an appropriate Specialist Team (or shared care) needs reconsideration. Much of the work of Specialist Services is now taken up with this six monthly review normally done by Psychiatrists or Specialist Nurses in secondary care. Â Most of these patients are stable and would not normally be in need of secondary care services. Â As a result an increasing amount of patients are unnecessarily taking up the services of secondary care. Â The NDS is encouraging referrals to Specialist Mental Health Services and with cuts in services, this monitoring role is causing major problems within Old Age Teams. Â This is against New Ways of Working. I therefore write to request that you	Comment noted. The recommendations in section 1 of the Final Appraisal Determination now include ‘regularly’ reviewed. The recommendations in section 1 of the Final Appraisal Determination allow for local shared care arrangements.

		consider:- 1)That there is no clinical reason why monitoring must be done every six months. Â Yearly is more appropriate and fits in with the dementia QOF. 2) Monitoring need not be provided by “Specialist Teams” and it should be seen as normal for this to be done in Primary Care (preferably as part of the dementia QOF). This would improve services for patients and would be more cost effective for the NHS. I can provide 2 papers on this subject.	
NHS Professional	Section 1	Please clarify re sequential use of memantine i.e. AChE for mild to mod, following on with memantine when severe. The guidance as is written could be interpreted to mean this is OK	Comment noted. Sections 1.1 and 1.2 of the Final Appraisal Determination recommends AChE inhibitors as options in mild to moderate disease and memantine as an option in severe disease and in moderate disease for those unable to take AChE inhibitors.
NHS Professional Consultant Physician	Notes	I have been involved in running memory clinics and assessing such patients for 10 years. The new guidance seems much more helpful and sensible than the previous advice. It will be very helpful to be able to clinically assess when drugs are needed and to be able to start them in early dementia when there is so much more scope for maintaining function and avoiding admission to institutions. I value the move from strict MMSE criteria. We will continue to use MMSE but some people of high intellect will score well even when quite demented and to be able to give treatment to them will be good.	Comment noted. The guidance now mentions those people with a high level of education.
NHS Professional Consultant Physician	Section 1	Very helpful guidance and much better for patients who will not have to wait until they are very muddled until they start treatment. The scope for improvement is greater early on and some patient can sustain a beneficial response for a number of years and thus reduce carer stress and the need for care. I value the guidance’s move from strict adherence to MMSE to a more holistic assessment which allows clinicians and patients and carers to focus upon important outcomes to them. Certainly some patients only increase their MMSE scores a little but the family report marked improvements in initiative and function. Being able to use ACEI in early dementia will give many people more chance of staying at home for longer. Sometimes in the past when	Comment noted.

		monitoring someone and waiting for deterioration they have gone into care before they have achieved a low enough MMSE to merit treatment. The ability to use ACEI early should keep more people at home, safely and comfortably for longer.	
NHS Professional Consultant Physician	Section 2	2.6 MMSE 26-21 usually defines mild dementia and below 30 possible MCI. Helpful comments overall. 2.8 ACEI at an early stage does seem to retard the relentless progression of cognitive failure in some people. As emphasised the non pharmacological management is important but most people would be glad to take something that might slow progress and improve symptoms.	A technical issue relating to the publication of the Appraisal Consultation Document on the website was corrected during the consultation period and the MMSE score was amended.
NHS Professional Consultant Physician	Section 3	It may be worth adding the prolonged release galantamine information to 3.4 as well as in 3.6 to the dosages and the information about rivastigmine patches in3.7 as well as in 3.9.	Comment noted. Galantamine prolonged release has been added to section 3 of the Final Appraisal Determination.
NHS Professional Consultant Physician	Section 4	I am delighted that you have moved from a cost effectiveness model based upon life prolongation to a more clinical/ patient significant model based upon quality of life and reduction in care costs.	Comment noted.
NHS Professional Consultant Physician	Section 5	It would be good to see the audit support tool	Audit support tools are issued with publication of the Final Appraisal Determination.
NHS Professional Chair – Dementia Governance Group of Care Trust	Section 1	The Dementia Governance Group at the Manchester Mental Health and Social Care Trust reviewed the draft guidelines. We are of the opinion that they are to be supported. However, we did feel that a small change should be made to the following sentence - "Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional and behavioural symptoms." We felt that the word and should be replaced with or so that the sentence reads "Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms." The rationale for this is that clinical experience suggests positive changes and benefit may occur in one or more domains but not necessarily in all. The magnitude of benefit in one area may well be greater than a lack of benefit in others and	The relevant wording of the recommendations in section 1.3 of the Final Appraisal Determination has been changed to global, functional 'or' behavioural symptoms.

		treatment would therefore be regarded as efficacious.	
NHS Professional Consultant Psychiatrist for Older People	Section 4	I use memantine and ACHEI combination therapy with success. I use it in younger onset patients, and in patients who we are trying to keep in a particular level of care e.g. at home as opposed to 24 hour care. I also use it after a patient has been on an ACHEI who as the disease progresses develop behavioural problems which memantine may specifically help e.g. aggression/psychosis. It would seem illogical to stop the ACHEI in these patients when they benefit different aspects of the patients symptoms e.g. cognition vs. behaviour. The two papers are also in different patient populations the initial Tariot paper in a more severe group and the latter on in a milder group. If you were to switch you would need a cross over period as well to make sure stopping the ACHEI did not have detrimental effects whilst initiating memantine. And despite theoretical concerns I see no clinical problems with memantine and galantamine, as is the case with colleagues I have spoken to about this.	NICE publishes recommendations based on the clinical and cost effectiveness of technologies. Prescribers should refer to the Summary of Product Characteristics for prescribing information. There was insufficient evidence to recommend combination treatment with AChE inhibitors and memantine.
NHS Professional	Section 1	The provisional recommendations extend recommended usage of the AChE inhibitors and memantine. Donepezil, galantamine and rivastigmine are now recommended for use in both mild and moderate Alzheimer's, rather than only in moderate Alzheimer's as per existing guidance (TA111). Memantine is recommended for use in people with moderate Alzheimer's who are intolerant of or have a contraindication to AChE inhibitors, and in severe Alzheimer's disease in TA111 it was not recommended for use outside of clinical trials.	Comment noted.
NHS Professional	Section 2	These recommendations could substantially increase the use and therefore the overall cost of this drug for a PCT population. There will be additional assessment costs. Implementing this guidance could carry drug costs of between £2.5 and £3 million annually for the average PCT. This represents an increase over and above current costs of about £1.5 to £1.7 million annually, about 1.5 times the estimated current costs based on existing guidance. These figures assume that all eligible prevalent patients in the PCT receive treatment for the full year. The AChE inhibitors cost between about £950 and £1,200 annually, and memantine about	Comment noted. NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		£850 annually (based on the Assessment Group's cost calculations, using BNF 59 drug costs). There may also be other costs of implementing the guidance, as treatment should only be initiated by specialists in the care of patients with dementia and additional assessments will increase clinic time. This additional resource will buy an extension of independent living of about one to two months for two to three thousand people per PCT, by delaying admission to institutional care, but it will not extend life.	
NHS Professional	Section 3	The new evidence found did not substantially change conclusions about the efficacy of the drugs. Seventeen new RCTs were identified in the updated review. In general they supported the effects of the AChE inhibitor treatments on cognitive, functional and global outcomes, and increased the amount and precision of the findings. There was insufficient evidence to suggest that there was any difference in effectiveness between the AChE inhibitors. In contrast to the one existing RCT of memantine identified in the previous review, the new memantine RCT identified in the current technology appraisal did not find a benefit for the drug compared with placebo. On pooling of the RCTs the improvements in global outcome seen in the previous review did remain, but mixed results were found for cognitive and functional outcomes. The manufacturer's meta analyses included more studies than the assessment group's analyses as they had individual patient data from their own trials in populations of mixed severity levels. These analyses also supported an effect for memantine. There is limited data available on long term outcomes, those needed for the cost effectiveness analyses. Few RCTs lasted longer than 6 months, or assessed the effects of treatment on institutionalisation, survival, or quality of life. The effects of the treatment on institutionalisation and survival are key parameters in the cost-utility analyses, there are assumptions underlying how these were modelled. There is substantial uncertainty about the cost effectiveness of these treatments. After making revisions based on comments received from consultees and commentators, the final Assessment Group analyses suggested that all of the drugs dominated best supportive care. However, in	The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.

		their initial analyses none of the drugs were cost effective, and had much higher ICERs. There was considerable uncertainty about the most appropriate modelling approach, and about the model parameters. For example, no information on institutionalisation was available from RCTs and had to be modelled based on data from a small UK cohort using the effects of the drugs on functional and cognitive outcomes. The major driver of cost effectiveness in the analyses is institutionalisation costs. In the final model, the AChE inhibitors were estimated to delay institutionalisation by between 1.4 and 1.7 months. The delay from using memantine was 0.8 months. Variability in the delay to institutionalisation input into models could have a large effect on the cost effectiveness of the treatments. The conditional requirements are unchanged from TA11 except that direct reference to the use of the MMSE to measure cognition has been removed. The AChE inhibitors, as assessed with the latest model, will not be cost effective use of NHS resources in people with dementia who are in institutional care or close to institutionalisation. PCTs might consider suggesting a further condition to the provisional recommendation, that the drugs should not be used in people within three months of institutionalisation or for those already in full time care. No new safety concerns have arisen since the previous technology appraisal. The adverse effects of the treatments are well established and include gastrointestinal effects for the AChE inhibitors	
NHS Professional	Section 4	There are limitations to the quality of the research. The quality of the new RCTs was described as moderate to poor. They had short durations and used methods of analysis that may overestimate the effects of treatment.	Comment noted. The Assessment Group conducted a review of evidence published since 2004. The final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004.
NHS Professional	Section 5	In light of the minimal additional evidence and the potential population need for this treatment further optimising of this recommendation is required	Comment noted.
NHS	Section 1	It is disappointing that NICE has changed its recommendations	NICE makes recommendations on the

Professional		on these medicines without additional new robust evidence to demonstrate their efficacy. It comes at a time when the NHS is facing severe financial challenge and these recommendations could substantially increase the costs of the drug and assessment clinics significantly. The technologies will not extend life but may buy an extension to independent living. This needs to be balance by disinvestment elsewhere in the health economy. It is a pity that the direct requirement to measure MMSE has been removed.	clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 4	The new evidence does not change the conclusions about efficacy. The quality of the research is generally poor. It therefore seems perverse to change the guidance. There is limited data on long term outcomes despite the drugs being used for a long time. There appears to be a lot of uncertainty about the cost effectiveness of these interventions. Any benefits are unlikely to be gained in the health sector.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 5	As indicated earlier, implementation will be a challenge in the face of financial situation in the PCT.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 6	Higher quality evidence is required.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base

			prior to 2004.
Patient	Section 1	The present restriction of only prescribing AChE inhibitors on the NHS when the patient's condition has progressed to Moderate AD condemns a patient with Mild AD to deteriorate to Moderate before a drug can be prescribed that will, at best, only hold the condition at that now advanced level. It must be beneficial to the patient and cost effective to start prescribing when the patient has a better quality of life which is then maintained by medication and they should not need nursing or hospital care.	Comment noted.
Carer	Section 1	You mention "physical, sensory or learning disabilities" etc that would artificially lower a score. You do not mention patients with e.g. a higher than average IQ or better than average language abilities that would artificially mask the effects of the disease.	The guidance now mentions those with a high level of education.
Carer	Section 2	2.6 - the scores for moderately , and moderately severe overlap, so a patient with a score of 11 could fall into both categories.	A technical issue relating to the publication of the Appraisal Consultation Document on the website was corrected during the consultation period and the MMSE score was amended.
NHS Professional	Section 8	Do NICE give sufficient consideration to the UK patent expiries of the medicines in their TAGs when setting review dates? The patents for Aricept, Reminyl and Exelon expire in Feb, Jan and Jul 2012 respectively and the likely ensuing fall in the price of generics will clearly affect the cost-effectiveness of AChE inhibitors from beyond 2012. Implementing wider use of AChE inhibitors in 2013 is likely to be considerably more affordable than it will be next year!	The guidance will be considered for review in April 2014.
NHS Professional Deputy Director Patient Safety	Section 2	These recommendations could substantially increase the use and therefore the overall cost of this drug for a PCT population. There will be additional assessment costs. Implementing this guidance could carry drug costs of between £2.5 and £3 million annually for the average PCT. This represents an increase over and above current costs of about £1.5 to £1.7 million annually, about 1.5 times the estimated current costs based on existing guidance. These figures assume that all eligible prevalent patients in the PCT receive treatment for the full year. There may also be other costs of implementing the guidance, as treatment should only be	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		initiated by specialists in the care of patients with dementia and additional assessments will increase clinic time. This additional resource will buy an extension of independent living of about one to two months for two to three thousand people per PCT, by delaying admission. Â This will increase pressure clinic service available and will result in longer waiting times for patients.	
NHS Professional Deputy Director Patient Safety	Section 3	The new evidence found does not substantially change conclusions about the efficacy of the drugs. Seventeen new RCTs were identified in the updated review. In general they supported the effects of the AChE inhibitor treatments on cognitive, functional and global outcomes, and increased the amount and precision of the findings. There was insufficient evidence to suggest that there was any difference in effectiveness between the AChE inhibitors.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional Deputy Director Patient Safety	Section 4	There are limitations to the quality of the research. The quality of the new RCTs was described as moderate to poor. They had short durations and used methods of analysis that may overestimate the effects of treatment.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004.
NHS Professional	Section 1	Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111) The considered opinion of the medicines management team in NHS Sheffield is that the provisional recommendations to extend the recommended usage of AChE inhibitors and memantine should be reconsidered. This will considerably increase pressure on	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		prescribing costs for limited clinical benefit. I am unable to identify exactly what services would have to be reduced in order to fund the predicted 2.3 to 2.6 million pound increased spend for Sheffield but the reductions would clearly need to be substantial. Given the acknowledged limited benefit that may result from this increase in expenditure it is difficult to see how this can be justified given the existing cost pressure within the NHS.	
NHS Professional	Section 2	NHS Sheffield has already identified significant usage of these agents outside existing NICE guidance and the provisional recommendations to extend the range of recommended usage of the AChE inhibitors and memantine will result in less control of prescribing for this group of patients. The removal of direct reference to the use of the MMSE to measure cognition will also significantly reduce options for clinical audit of patient selection and management.	The MMSE specification has been removed from the guidance recommendations in the Final Appraisal Determination. In TA111 it was highlighted that there were equality issues in relation to the use of the MMSE.
NHS Professional	Section 4	The provisional recommendations will substantially increase the usage of these drugs, which I estimate will result in increased costs in Sheffield of between 2.3 and 2.6 million pounds. There will also be further costs of implementing the guidance, as treatment should only be initiated by specialists in the care of patients with dementia and the extension of the range of severity that can be treated will generate additional assessments which will increase outpatient appointments and follow-ups. This additional resource will only generate an extension of independent living of approximately one to two months for two to three thousand people per PCT, by delaying admission to institutional care, but it will not extend life. The new evidence examined did not substantially change conclusions about the overall efficacy of the drugs or any difference between the individual drugs. There is very little data available on long term outcomes, or the effects of treatment on institutionalisation, survival, or quality of life.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
	Section 5	In summary I would like NICE to reconsider this provisional recommendation. If it is politically difficult to restrict the entry level of severity that triggers treatment then there should be clear assessment criteria specified in the guidance and clear guidance	The MMSE specification has been removed from the guidance recommendations. In TA111 it was highlighted that there were equality issues

		for when the drugs should be discontinued. Direct reference to MMSE should be reinstated and if the use of AChE inhibitors were assumed to stop on institutionalisation this should be clarified along with any other discontinuation criteria e.g. sudden and rapid decline in MMSE.	in relation to the use of the MMSE.
NHS Professional	Notes	I have been a carer for a person with dementia and in addition I have supported a family member who was looking after a person with dementia. I therefore offer these views from that perspective as well as from a professional perspective.	Comment noted
NHS Professional	Section 1	The provisional recommendations extend recommended usage of the AChE inhibitors and memantine. Donepezil, galantamine and rivastigmine are now recommended for use in both mild and moderate Alzheimer's, rather than only in moderate Alzheimer's as per existing guidance (TA111). Memantine is recommended for use in people with moderate Alzheimer's who are intolerant of or have a contraindication to AChE inhibitors, and in severe Alzheimer's disease in TA111 it was not recommended for use outside of clinical trials. As a carer for a patient with dementia I want NICE to understand that drugs instead of care will be a loss not a benefit. The support received by the patient (to come to terms with their disease at the early stages and plan for the future) and for carers (particularly later in the disease) brings a far greater benefit in terms of the well being of both patient and carer. A visit from a person who understands what a carer is coping with, and who has resources to offer such as day care or help at home with washing, dressing and feeding is so much more important in overall management of this disease	Comment noted. NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact. The NICE clinical guideline makes recommendation on the care of people with dementia.
NHS Professional	Section 2	These recommendations could substantially increase the use and therefore the overall cost of this drug for a PCT population. There will be additional assessment costs. Implementing this guidance would bring an increase over and above current costs of about £1.5 to £1.7 million annually. There may also be other costs of implementing the guidance, as treatment should only be initiated by specialists in the care of patients with dementia and additional assessments will increase clinic time. Within my PCT we are planning for 2011 extra services for patients with dementia and	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		their carers in partnership between Older Peoples Mental Health services and GP practices. The new service will help carers and patients towards the later stages of this disease when it is very hard to cope with. If implemented this guidance would mean we would not have money to run this extra service. Having seen a close friend manage their spouse in the later stages of dementia I know he would feel devastated to know that services that these vital services in the later stages would be put at risk by NICE in exchange for only one or two months extra before a patient was totally dependent on others	
NHS Professional	Section 3	The new evidence found did not substantially change conclusions about the efficacy of the drugs. The adverse effects of the treatments are well established and include gastrointestinal effects for the AChE inhibitors. Too little weight is given to the difficulty these side effects have on carers. The AChE inhibitors, as assessed with the latest model, will not be cost effective use of NHS resources in people with dementia who are in institutional care or close to institutionalisation. PCTs might consider suggesting a further condition to the provisional recommendation, that the drugs should not be used in people within three months of institutionalisation or for those already in full time care. In the final model, the AChE inhibitors were estimated to delay institutionalisation by between 1.4 and 1.7 months. The delay from using memantine was 0.8 months. Variability in the delay to institutionalisation input into models could have a large effect on the cost effectiveness of the treatments. This is NOT a good enough basis on which to effectively make PCTs stop services that support carers because all the money will have gone to drugs.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 4	The conditional requirements are unchanged from TA111 except that direct reference to the use of the MMSE to measure cognition has been removed. Local experience has proven that taking this reference out will make it much harder for GPs to be involved in ongoing assessment and so will increase costs on drugs continued inappropriately and in specialist clinics to assess drugs. This is a waste when the money is needed to support	The MMSE specification has been removed from the guidance recommendations. In TA111 it was highlighted that there were equality issues in relation to the use of the MMSE.

		carers. The AChE inhibitors, as assessed with the latest model, will not be cost effective use of NHS resources in people with dementia who are in institutional care or close to institutionalisation. Please, please add a condition to the provisional recommendation, that the drugs should not be used in people within three months of institutionalisation or for those already in full time care.	
NHS Professional	Section 5	There are limitations to the quality of the research. The quality of the new RCTs was described as moderate to poor. They had short durations and used methods of analysis that may overestimate the effects of treatment, so why is NICE using this to spend £millions on drugs that is needed for care services for these people. The audit "support" generally creates perverse conditions for patients - pushing drugs rather than looking at the needs of the whole patient and carer partnership and their interdependencies. NICE is wrong to produce guidance that does not acknowledge the substantial cost and the effect that certainly will have on other services that cannot therefore be provided for people with dementia and their carers. For dementia NICE needs to acknowledge the real world of people caring at home for those with dementia and think about how they will be disadvantaged by spending an enormous amount of money preferentially on the drugs for benefits that are minimal compared to the overall time a patient will be suffering from dementia. PCTs and councils will not have the money for drugs and care. Please can we have more care and less drug use.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease. NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 6	6. The relative impact on carers and patients of services other than drugs should be quantified so that when we look at value based pricing of drugs the drugs are compared properly with the alternatives that make much more difference overall to the care of people with dementia AND THEIR CARERS	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS	Section 7	This TAG will mean that there will not be money available across	NICE makes recommendations on the

Professional		the NHS to implement the good practice in the CG. That is perverse NICE needs to issue guidance that takes proper account of the opportunity cost of their guidance.	clinical and cost effectiveness of technologies and does not consider budget impact.
Other Effectiveness and clinical audit	Section 1	The considered opinion of the medicines management team in NHS Sheffield is that the provisional recommendations to extend the recommended usage of AChE inhibitors and memantine should be reconsidered. This will considerably increase pressure on prescribing costs for limited clinical benefit. I am unable to identify exactly what services would have to be reduced in order to fund the predicted 2.3 to 2.6 million pound increased spend for Sheffield but the reductions would clearly need to be substantial. Given the acknowledged limited benefit that may result from this increase in expenditure it is difficult to see how this can be justified given the existing cost pressure within the NHS. NHS Sheffield has already identified significant usage of these agents outside existing NICE guidance and the provisional recommendations to extend the range of recommended usage of the AChE inhibitors and memantine will result in less control of prescribing for this group of patients. The removal of direct reference to the use of the MMSE to measure cognition will also significantly reduce options for clinical audit of patient selection and management.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
Other Effectiveness and clinical audit	Section 2	The provisional recommendations will substantially increase the usage of these drugs, which I estimate will result in increased costs in Sheffield of between 2.3 and 2.6 million pounds. There will also be further costs of implementing the guidance, as treatment should only be initiated by specialists in the care of patients with dementia and the extension of the range of severity that can be treated will generate additional assessments which will increase outpatient appointments and follow-ups. This additional resource will only generate an extension of independent living of approximately one to two months for two to three thousand people per PCT, by delaying admission to institutional care, but it will not extend life.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
Other	Section 4	The new evidence examined did not substantially change	The Assessment Group conducted a

Effectiveness and clinical audit		conclusions about the overall efficacy of the drugs or any difference between the individual drugs. There is very little data available on long term outcomes, or the effects of treatment on institutionalisation, survival, or quality of life. In summary I would like NICE to reconsider this provisional recommendation. If it is politically difficult to restrict the entry level of severity that triggers treatment then there should be clear assessment criteria specified in the guidance and clear guidance for when the drugs should be discontinued. Direct reference to MMSE should be reinstated and if the use of AChE inhibitors were assumed to stop on institutionalisation this should be clarified along with any other discontinuation criteria e.g. sudden and rapid decline in MMSE.	review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 2	These recommendations could substantially increase the use and therefore the overall cost of this drug for a PCT population. There will be additional assessment costs. I feel it is relevant to highlight that This additional resource will buy an extension of independent living of about one to two months for two to three thousand people per PCT, by delaying admission to institutional care, but it will not extend life.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 3	The new evidence found did not substantially change conclusions about the efficacy of the drugs. In contrast to the one existing RCT of memantine identified in the previous review, the new memantine RCT identified in the current technology appraisal did not find a benefit for the drug compared with placebo. There is limited data available on long term outcomes and There is substantial uncertainty about the cost effectiveness of these treatments. The AChE inhibitors, as assessed with the latest model, will not be cost effective use of NHS resources in people with dementia who are in institutional care or close to institutionalisation. Suggest that the drugs should not be used in people within three months of institutionalisation or for those	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty.

		already in full time care.	Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 4	It is worth noting that there are limitations to the quality of the research. The quality of the new RCTs was described as moderate to poor. They had short durations and used methods of analysis that may overestimate the effects of treatment.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 6	Supported.	Comment noted
NHS Professional	Section 8	Would suggest three years was more appropriate to ensure any new research evidence is appraised in a timely manner.	The guidance will be considered for review in April 2014.
NHS Professional Public Health Registrar	Section 2	There is an associated cost with implementing proposed changes – in Bradford and Airedale the extra drug costs are likely to be between £420,000 and £1,032,000, with further costs likely due to increasing service capacity. NHS is facing significant financial challenges, with little growth in budgets – with the required increase on drugs spend on drugs for mild Alzheimer's disease, there will need to be disinvestment from existing services. This disinvestment may come from within the current dementia	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		budget, from the wider mental health budget or from within another programme budget area, however, no matter where the disinvestment is, the opportunity cost of alterations to the NICE guidance will be evident.	
NHS Professional Public Health Registrar	Section 3 (The technologies)	The use of AChE inhibitors is partly to promote independent living and, therefore should only be used for those who are currently living independently – if given to persons living in institutional care or close to requiring care, is unlikely to be cost effective. Anti-psychotics are currently being widely prescribed off-license for behavioural symptoms associated with dementia - move towards wider prescribing of AChE inhibitors may lead to a reduction in prescriptions of anti-psychotics.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional Public Health Registrar	Section 4	Quality of evidence. The quality of evidence on which the new guidance has been based has been described by NICE as moderate to poor (short follow up and little evidence on survival, institutionalisation or quality of life). The model suggests that AChE inhibitors delays institutionalisation by around a year and a half, although the evidence base is sparse. Accordingly there is much uncertainty around the cost per QALY	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional Public Health Registrar	Section 5	Local impact. Significant numbers of people have dementia but are undiagnosed. Under-diagnosis is likely to be mainly within people with mild disease and, therefore, the impact of proposed NICE guidelines will, in part, depend locally on how well we do at identifying currently undiagnosed disease. Estimated that of those with dementia, between 885 and 1,719 people will have mild Alzheimer's disease. Assuming that no-one with mild	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		disease is currently receiving treatment, the drug costs associated with treating these individuals is likely to be between £420,000 and £1,032,000 a year. In addition to prescribing costs there is likely to be a cost associated with an increase in specialist clinic appointments. In contrast it may reduce the number of people requiring to live within social care settings. Likely that the number of people diagnosed with Alzheimer's disease will also increase as: A treatment can be used for mild dementia and therefore GPs may be more likely to diagnose. The introduction of memory assessment centres is likely to result in more identification. The population is ageing.	
NHS Professional	Section 1	The provisional recommendations extend recommended usage of the AChE inhibitors and memantine. This is despite the new evidence reviewed failing to substantially change conclusions about the efficacy of the drugs.	The Assessment Group conducted a review of evidence published since 2004. The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 2	These recommendations could substantially increase the use and therefore the overall cost of this drug for a PCT population. There will be additional assessment costs. Implementing this guidance could carry drug costs of between £2.5 and £3 million annually for the average PCT. This represents an increase over and above current costs of about £1.5 to £1.7 million annually, about 1.5	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		times the estimated current costs based on existing guidance. These figures assume that all eligible prevalent patients in the PCT receive treatment for the full year. The AChE inhibitors cost between about £950 and £1,200 annually, and memantine about £850 annually (based on the Assessment Group's cost calculations, using BNF 59 drug costs). There may also be other costs of implementing the guidance, as treatment should only be initiated by specialists in the care of patients with dementia and additional assessments will increase clinic time. This additional resource will buy an extension of independent living of about one to two months for two to three thousand people per PCT, by delaying admission to institutional care, but it will not extend life.	
NHS Professional	Section 3	The new evidence found did not substantially change conclusions about the efficacy of the drugs. Seventeen new RCTs identified - in general they supported the effects of the AChE inhibitor treatments on cognitive, functional and global outcomes, and increased the amount and precision of the findings. There was insufficient evidence to suggest that there was any difference in effectiveness between the AChE inhibitors. In contrast to the one existing RCT of memantine identified in the previous review, the new memantine RCT identified in the current technology appraisal did not find a benefit for the drug compared with placebo. There is limited data available on long term outcomes, those needed for the cost effectiveness analyses. The effects of the treatment on institutionalisation and survival are key parameters in the cost-utility analyses, there are assumptions underlying how these were modelled. Therefore, there is substantial uncertainty about the cost effectiveness of these treatments. No new safety concerns have arisen since the previous technology appraisal.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 4	There are limitations to the quality of the research. The quality of the new RCTs was described as moderate to poor. They had short durations and used methods of analysis that may overestimate the effects of treatment.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004.

			The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 5	In agreeing to fund, or extend access to, one treatment or service, there is always opportunity cost within finite resources. This opportunity cost may have an impact on the PCTs ability to provide any of a range of treatments and services, depending on the PCTs current priorities for commissioning. In order to fund extended access to treatments for Alzheimer's, in line with these provisional recommendations (approximately £1.5 million in additional expenditure), NHS Dorset will need to consider where further efficiencies or savings can be gained. We may need to further restrict procedures that are considered a lower priority.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional GP	Notes	Will the committee please comment on the cost effectiveness on continuing to prescribe these drugs to patients who are ALREADY institutionalised in care homes? Some guidance on this would be very useful.	The recommendations are for mild, moderate and severe Alzheimer's disease and do not refer to whether a person is in an institution.
NHS Professional GP	Section 1	Will the committee please comment on the cost effectiveness on continuing to prescribe these drugs to patients who are ALREADY institutionalised in care homes? Some guidance on this would be very useful.	The recommendations are for mild, moderate and severe Alzheimer's disease and do not refer to whether a person is in an institution.
NHS Professional	Section 1	Oxfordshire PCT currently spends over £900,000 a year on drugs for AD. We are also aware that only about 30% of expected patients have a diagnosis and in the next year we expect a further 900 patients to be diagnosed. Extending treatment as suggested above is likely to cost a further £2.16 million for the drugs PLUS the requirement to at least double the number of clinics and specialist staff. The criterion having a worthwhile	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.

		effect on cognitive, global, functional and behavioural symptoms is far too vague - guidance MUST state how this is to be established - locally we use both MMSE and BADL-S but other scores are also helpful. Patient progress cannot be assessed unless there are criteria to assess them against. Worthwhile is not useful to anyone, including patients and carers.	
NHS Professional	Section 2	Clinical and social needs for these patients and their carers are high and non-pharmacological interventions, especially early on in the disease are effective e.g. "early provision of support at home can decrease institutionalisation by 22%" (Gaugler JE, Kane RL, Kane RA and Newcomer R (2005). 'Early Community-Based Service Utilization and Its Effects on Institutionalization in Dementia Caregiving'. The Gerontologist, 45, 177–185.) Good supporting treatments should not be compromised or prevented because all the available money is being spent upon drugs which may have less useful effects on ADLs. MMSE, whilst a useful research tool, is less helpful in predicting how the activities of daily living of a patient will be affected by the disease and thus functional severity. However, assessment scores are still needed to be able to measure how a patient is responding. This should be included.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 3	This section would appear to be accurate. It would be helpful if annual costs for the drugs could also be included e.g. £1,164 for donepezil 10mg daily, £966 for galantamine 16-24mg daily, £1,176 for rivastigmine 9-12mg daily and £852 for memantine 15-20mg daily.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 4	Patients live with AD for a median of 6 years and expansion of the patient group to be treated will result in patients receiving these drugs long term despite very limited data for long term efficacy (trials lasting no longer than 24 weeks). The quality of the research is described as moderate to poor. There are considerable uncertainties around cost effectiveness with large variations depending on the parameters. The NHS could thus be spending a huge amount of money which is better spent on other interventions for these patients with poor outcomes of low cost-effectiveness. The opportunity costs with drugs are very high.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact. The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base

		There are assumptions that treatment stops on institutionalisation which in our experience locally is not the case. Patients continue to receive ACHEIs in the hope that they control behavioural symptoms which are otherwise untreatable. This completely negates the basis that the drugs have their cost-effectiveness calculated on lengthening the time to residential care.	prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 5	Oxfordshire currently has memory clinics operated by both the acute and mental health provider trusts. We have estimated that only about a third of anticipated numbers of patients currently has a diagnosis. Increasing the number of diagnoses and ensuring 6 monthly review will require a much larger number of clinics, employment and training of specialist nurses and GPSIs to relieve the burden on consultants and to ensure that patients can access treatment equitably. This will not be possible if the funding directive stands at 3 months - current estimates suggest that a further 900 patients would be seen, under the previous NICE TA only 200 of these would have been eligible for treatment. This PCT would be unable to implement the required changes within 3 months.	Comment noted. The recommendations in section 1 of the Final Appraisal Determination now read 'regular' review.
NHS Professional	Section 7	The extension of treatment with these drugs to a wider patient group will take funds away from other interventions which have been identified within the clinical guideline.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 1	1.1 The recommendation that cholinesterase inhibitors be used within their licensed indication, including mild dementia, is welcome. The requirement for review of patients who are prescribed cholinesterase inhibitors by a specialist team every six months is costly and unnecessary. It undervalues the skills of primary care teams and diverts secondary care resources for	The recommendations in section 1.4 of the Final Appraisal Determination allow for local shared care arrangements.

		specialist dementia care away from the patients with more severe illness and more challenging behaviours. The review of such patients should be carried out in primary care.	
NHS Professional	Section 1	The provisional recommendations extend recommended usage of the AChE inhibitors and memantine. Donepezil, galantamine and rivastigmine are now recommended for use in both mild and moderate Alzheimer's, rather than only in moderate Alzheimer's as per existing guidance (TA111). Memantine is recommended for use in people with moderate Alzheimer's who are intolerant of or have a contraindication to AChE inhibitors, and in severe Alzheimer's disease in TA111 it was not recommended for use outside of clinical trials.	Comment noted.
NHS Professional	Section 2	These recommendations could substantially increase the use and therefore the overall cost of this drug for a PCT population. There will be additional assessment costs. Implementing this guidance could carry drug costs of between £2.5 and £3 million annually for the average PCT. This represents an increase over and above current costs of about £1.5 to £1.7 million annually, about 1.5 times the estimated current costs based on existing guidance. These figures assume that all eligible prevalent patients in the PCT receive treatment for the full year. The AChE inhibitors cost between about £950 and £1,200 annually, and memantine about £850 annually (based on the Assessment Group's cost calculations, using BNF 59 drug costs). There may also be other costs of implementing the guidance, as treatment should only be initiated by specialists in the care of patients with dementia and additional assessments will increase clinic time. This additional resource will buy an extension of independent living of about one to two months for two to three thousand people per PCT, by delaying admission to institutional care, but it will not extend life.	NICE makes recommendations on the clinical and cost effectiveness of technologies and does not consider budget impact.
NHS Professional	Section 3	The new evidence found did not substantially change conclusions about the efficacy of the drugs. Seventeen new RCTs were identified in the updated review. In general they supported the effects of the AChE inhibitor treatments on cognitive, functional and global outcomes, and increased the amount and precision of the findings. There was insufficient evidence to suggest that there	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004.

		was any difference in effectiveness between the AChE inhibitors. In contrast to the one existing RCT of memantine identified in the previous review, the new memantine RCT identified in the current technology appraisal did not find a benefit for the drug compared with placebo. On pooling of the RCTs the improvements in global outcome seen in the previous review did remain, but mixed results were found for cognitive and functional outcomes. The manufacturer's meta analyses included more studies than the assessment group's analyses as they had individual patient data from their own trials in populations of mixed severity levels. These analyses also supported an effect for memantine. This comment continues from section 3 as there was not enough space. There is substantial uncertainty about the cost effectiveness of these treatments. After making revisions based on comments received from consultees and commentators, the final Assessment Group analyses suggested that all of the drugs dominated best supportive care. However, in their initial analyses none of the drugs were cost effective, and had much higher ICERs. There was considerable uncertainty about the most appropriate modelling approach, and about the model parameters. For example, no information on institutionalisation was available from RCTs and had to be modelled based on data from a small UK cohort using the effects of the drugs on functional and cognitive outcomes. The major driver of cost effectiveness in the analyses is institutionalisation costs. In the final model, the AChE inhibitors were estimated to delay institutionalisation by between 1.4 and 1.7 months. The delay from using memantine was 0.8 months. Variability in the delay to institutionalisation input into models could have a large effect on the cost effectiveness of the treatments.	The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.
NHS Professional	Section 4	The conditional requirements are unchanged from TA11 except that direct reference to the use of the MMSE to measure cognition has been removed. The AChE inhibitors, as assessed with the latest model, will not be cost effective use of NHS resources in people with dementia who are in institutional care or close to institutionalisation. PCTs might consider suggesting a	The economic model produced by the Assessment Group made the assumption that being in an institution was equivalent to severe disease. Therefore, this issue is discussed in the evidence section. However, this is not mentioned in the

		further condition to the provisional recommendation, that the drugs should not be used in people within three months of institutionalisation or for those already in full time care. No new safety concerns have arisen since the previous technology appraisal. The adverse effects of the treatments are well established and include gastrointestinal effects for the AChE inhibitors. There are limitations to the quality of the research. The quality of the new RCTs was described as moderate to poor. They had short durations and used methods of analysis that may overestimate the effects of treatment.	recommendations sections 1.1 to 1.6 of the Final Appraisal Determination and it is not intended that in clinical practice, severity is equated to living in an institution.
NHS Professional	Section 6	There is limited data available on long term outcomes, those needed for the cost effectiveness analyses. Few RCTs lasted longer than 6 months, or assessed the effects of treatment on institutionalisation, survival, or quality of life. The effects of the treatment on institutionalisation and survival are key parameters in the cost-utility analyses, there are assumptions underlying how these were modelled.	The Assessment Group conducted a review of evidence published since 2004. However, the final estimates of clinical effectiveness were based on pooled estimates with the existing evidence base prior to 2004. The evidence added to the existing knowledge about the benefits of AChE inhibitors and memantine and reduced the uncertainty. Improvements to the modelling better estimated that the AChE inhibitors were cost saving and memantine cost effective in severe disease and against best supportive care in moderate disease.