

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111)

Eisai/Pfizer Response to the Appraisal Consultation Document (ACD)

28th October 2010

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 therapy results in a rapid loss of these benefits.

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.

The draft guidance from NICE is long overdue and ensures that AD patients receive the only licensed pharmacological treatments available to treat the symptoms of AD.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.

- 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.

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 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).

- 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.

- 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 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 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.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

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

group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

None.

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