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

Dear Kate,

Many thanks for the opportunity for Novartis to review the Appraisal Consultation Document (ACD) for the above appraisal. Please find overleaf our detailed comments.

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:

1. Further discussion of drug interactions is warranted
2. Incorrect drug acquisition costs are quoted in the ACD
3. Misleading description of the 9.5 cm^2 rivastigmine patch as a 'lower dose patch'

If you have any questions or require further information please don't hesitate to get in touch with me.

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.[1] Furthermore, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.[1]

Donepezil is metabolised by the cytochrome P450 system.[2] 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 the levels of donepezil.[2] Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care.[2]

Galantamine is partially metabolised by various cytochromes, mainly CYP2D6 and CYP3A4.[3] 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.[3]"

For a succinct summary of drug interactions Novartis would like to draw your attention to the 10th edition of the Maudsley Guidelines[4] page 393.

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 were based on the BNF edition 58 and ranged from £79 for rivastigmine patches to £97 for donepezil."

3. Misleading description of the 9.5 cm^2 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)."*

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[1] Exelon® (rivastigmine) Summary of Product Characteristics. April 2010.
[2] Aricept ® (donepezil) Summary of Product Characteristics. May 2009.
[3] Reminyl ® (Galantamine) Summary of Product Characteristics. March 2010.
[4] Taylor D et al. (2009) The Maudsley Prescribing Guideline, 10th Revised edition. Infoma Healthcare.