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PBS Post-Market
Department of Health and Ageing
MDP 900
GPO Box 9848
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Re: Review of Pharmaceutical Benefits Scheme anti-dementia drugs to treat Alzheimers Disease

To Whom It May Concern,

Thank you for providing Novartis Pharmaceuticals Australia with the opportunity to contribute to the review of medicines used in the treatment of Alzheimers disease.

Novartis manufactures and distributes rivastigmine (Exelon® oral solution, capsules and Exelon® transdermal patch), one of only four anti-dementia drugs available in Australia that are approved for the treatment of mild to moderately severe Alzheimer's disease.

Rivastigmine capsules were recommended for PBS listing by the PBAC in December 2000 (at the same meeting as donepezil). Rivastigmine oral solution was recommended for PBS listing in June 2001 with the same listing criteria as rivastigmine capsules. Two strengths of the transdermal patch were recommended for PBS listing by the PBAC in March 2008. The restriction wording for Exelon® patch was the same as for Exelon® capsules and oral solution. Over the years since the original listing, the restriction wording has been modified slightly. However, the basis for measuring treatment benefit has not been altered.

Dementia is a progressive neurologic condition for which there is presently no cure. Alzheimer's disease is the most common type of dementia and is the largest cause of disability in older Australians[1]. Dementia and therefore Alzheimer's disease is recognised as a national epidemic[2]. Novartis welcomes the Government's proposal to consider dementia as a future National Health Priority[3] and is encouraged by the scope of the Inquiry into Dementia by the House of Representatives Standing Committee on Health & Ageing[4].

[1] http://www.fightdementia.org.au/media/key-facts-and-statistics-for-media.aspx
[2] Living longer, Living Better, Productivity Commission's Caring for Older Australians Report 2012
[3] Standing Council on Health (2012). Communique 27th April 2012.
[4] http://www.aph.gov.au/Parliamentary_Business/Committees/House_of_Representatives_Committees?url=haa/dementia/index.htm

Alzheimer's disease has a significant impact on caregivers[5]. Administering and managing medications is one of their many daily tasks. Exelon® patch is the only transdermal patch currently available to Alzheimer's patients. A prospective outcome of the IDEAL (Investigation of TransDermal Exelon in ALzheimer's disease) trial evaluated caregiver preference for rivastigmine patches compared with capsules. The results from this 24-week, randomised, double-blind, double-dummy, placebo- and active-controlled trial showed that caregivers had greater satisfaction overall ($p < 0.0001$) and less interference with daily life ($p < 0.01$) with the patch vs capsules[6]. Reduced caregiver stress, substantiated by greater satisfaction and less interference with daily life likely improves compliance with therapy. This is important since treatment compliance is relatively poor in this patient group and therefore patients may not be realising the full benefits of treatment[7]. Exelon® patch, offering comparable efficacy, improved compliance and preferred by carers is therefore unique within the group of medicines used in the treatment of Alzheimers disease.

The PBS listed medicines included in this review (donepezil; rivastigmine; galantamine; and memantine) are, at present, the only anti-dementia drugs available in Australia that are approved for the treatment of mild to moderately severe Alzheimer's disease (but not other causes of dementia). All four drugs are 'authority required', requiring diagnosis by a medical specialist, along with baseline cognitive and/or functional test results. The authority form must include the result of the baseline Mini-Mental State Examination (MMSE) and, if this result is at least 25 points, the result of the baseline Alzheimer's Disease Assessment Scale, cognitive sub-scale (ADAS-cog). Continuation on any of the drugs must be based on positive changes on the MMSE within 6 months.

The current continuation criteria, employing the MMSE as a surrogate for measuring treatment benefit, were a pragmatic choice based on the advice from a group of six specialist clinicians attending a stakeholder meeting in October 2000. This followed a request from the PBAC for simple stopping rules which target the drug to patients who experience an unambiguous, substantial clinical improvement on treatment[8]. At this stakeholder meeting, the specialists recommended testing only for cognition, given the requirement to keep the criteria simple. The MMSE also has the additional benefit of being understood and used by the medical community and taking significantly less time than alternative measures (for example the ADAS-cog). When compared with clinical diagnosis of Alzheimer's disease, the MMSE has a sensitivity of 0.75 and specificity of 0.82[9]. However, it is noted that early draft PBAC guidelines for therapy commencement and continuation recognised that treatment benefit is multi-faceted: "Patients must be reassessed within 6 months of commencing a drug for Alzheimer's disease. The aim of the reassessment is to determine whether the drug is of benefit ... Benefits may occur in cognition or function"[10].

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[5] The Dementia Epidemic: Economic Impact and Positive Solutions for Australia, Access Economics, 2003.

[6] Blesa R, Ballard C, Orgogozo JM, Lane R, Thomas SK. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. Neurology 69(4 Suppl 1):S23-8, 2007.

[7] Alzheimer's Australia. Alzheimer's Australia Consumer Medication Survey. 2005; Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, Nagel J et al. IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology 69(4 Suppl 1):S14-22, 2007.

[8] Excerpt from PBAC meeting minutes September 2000

[9] Makinnon et al (1998) Mackinnon A, Mulligan R. Combining cognitive testing and informant report to increase accuracy for dementia. Am J Psychiatry 1998;155:1529-35.

[10] Excerpt from draft PBAC guidelines for commencement and continuation of cholinesterase inhibitors used to treat mild to moderate Alzheimer's Disease, June 2000

When comparing access arrangements in countries with similar reimbursement systems to Australia we note that these countries have treatment continuation criteria which are not solely based on cognitive function but also include behavioural outcomes[11]. As the Terms of Reference (b) for this current review indicate an examination of alternate measures of patient relevant outcomes, we would suggest that any proposed changes to the current treatment restrictions would need to be assessed in the following context:

a) research into the sensitivity of the new process or instrument to changes in Alzheimer's disease to ensure equity of access to patients
b) acceptability of the changes to the medical profession both in terms of the time the assessment for the new continuation rule to be completed and the clinical validity of the continuation rule (ie does the required change make clinical sense) and
c) whether any additional administration costs associated with making changes to the restrictions and the management of the process are cost effective.

The Terms of Reference (c) also indicate the intention of the review to determine if there is more recent evidence on the safety and efficacy of these drugs. The safety, effectiveness and cost-effectiveness of anti-dementia drugs have been the subject of numerous publications, including systematic reviews, since these agents were first listed on the PBS. A Cochrane review[12] first published in 2006 has been reprinted in 2012 without change, suggesting that it is unlikely the Department will find additional information on the safety and efficacy of cholinesterase inhibitors (CEIs) in particular. The Cochrane review showed CEIs to be effective in improving patient outcomes based on measures of cognition (both MMSE and ADAS-cog) and also behavioural outcomes using both behavioural inventories (NPI) and structured clinical assessment involving carer input (CIBIC-plus).

With regard to cost effectivess, it is unlikely there is a more recent, comprehensive and robust analysis of the effectiveness and cost-effectiveness of these agents available in the published literature than the recently published health technology review by the PenTAG group in the UK[13]. The objective of this review was to provide updated guidance to the NHS on the clinical effectiveness and cost-effectiveness of agents for the treatment of Alzheimer's disease following their approval by NICE issued in November 2006 (amended September 2007, August 2009 and March 2011). The PenTAG review reported there is a greater than 99% probability that CEIs are more cost-effective than best supportive care and that CEIs are probably cost saving at a willingness-to-pay (WTP) of £30,000 per quality adjusted life-year (QALY) for people with mild-to-moderate Alzheimer's disease.

Finally, it is the stated intent of Terms of Reference (d) to review the current PBS restrictions and the likely effect it has on cost-effective utilisation of these medicines. The 2010/11 DUSC review concluded that [treatment] response, reported as an improvement in cognition, is

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[11] http://www.health.gov.bc.ca/pharmacare/adti/clinician/pdf/SECTION%203%20-%20Algorithms.pdf accessed 28/06/2012.
http://guidance.nice.org.uk/TA217/Guidance/pdf/English

[12] Birks J. Cholinesterase inhibitors for Alzheimer's Disease. Cochrane Database of Systematic Reviews 2006. Issue 1. Art No: CD 005593. DOI:10.1002/14651858. CD005593. (reprinted 2012).

[13] Bond et al (2012) Health Technol Assess. 2012;16(21):1-470.

much greater in the Australian setting[14]. The comparison was being made to the response rates reported in clinical trials. It may therefore be argued that since the observed response rates in Australia are higher, the implications for cost effectiveness are more positive than predicted at time of listing application. Indeed higher response rates, indicative of improved cognitive function which is a known determinant of nursing home admission avoidance[15], may in fact be cost saving to the Govenrment.

Novartis Pharmaceuticals Australia thanks the Department for the opportunity to contribute to this review and is happy to provide any further information. We look forward to receiving a copy of the review report for comment prior to it being considered by the PBAC in November 2012.

Yours sincerely,

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[14] Le Couteur, D. G., Robinson, M., Leverton, A., Creasey, H., Waite, L., Atkins, K. and McLachlan, A. J. (2011), Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer's disease. Australasian Journal on Ageing

[15] Coughlin TA, McBride TD, Liu K. (1990) Determinants of transitory and permanent nursing home admissions, Med Care. Jul;28(7):616-31.