1. Recent Australian utilisation data on patient initiation and continuation rates

1.a Review of PBS subsidised anti-dementia drugs prepared for the Drug Utilisation Subcommittee

Lundbeck Australia urges caution in interpretation and extrapolation of the data in general, and believes that the report's conclusions cannot be applied to EBIXA® (memantine) specifically.

The review of PBS-subsidised anti-dementia drugs 2004-2007, prepared for the Drug Utilisation Subcommittee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) investigated the extent and patterns of dispensing of PBS-listed choline esterase inhibitors (CEIs) in Australia during the period 2004 to 2007[1,2]. The review included details of dispensed CEIs donepezil, rivastigmine and galantamine for patients initiating treatment during 2004. These medications are PBS-listed for mild to moderately severe Alzheimer's disease (AD). EBIXA was PBS listed in July 2008 after the review period; hence, the review did not investigate EBIXA utilisation. To Lundbeck Australia's knowledge, such a review of PBS-listed EBIXA has never been undertaken.

EBIXA differs from the CEIs in two important aspects:

1- It has a different mechanism of action, being an N-methyl-D-aspartate antagonist, and is only PBS-listed for moderately severe to severe AD. Hence the findings of the DUSC review may not be representative of utilisation of PBS-listed EBIXA.

2- In addition, the review followed a cohort of patients who commenced treatment approximately eight years ago, and it is possible that with increasing experience with dementia therapy utilisation trends may be different for patients who commence treatment in 2012.

Among the key conclusions of the review were that overall utilisation of CEIs in terms of the proportion of the population, duration, persistence and

adherence is similar to that reported in other countries, the major difference being response reported as an improvement in cognition was much greater in the Australian setting.

Although it is uncertain how these conclusions relate to EBIXA utilisation in Australia, restrictions for initial and continuing reimbursed use of EBIXA are displayed in Table 1, which outlines initial and continuation criteria for reimbursed access to EBIXA in Australia and 17 European countries.

Although requirements vary considerably between countries; it is worth noting that in major EU countries the requirements in terms of continuation criteria are far less onerous. Apart from Italy, none of the remaining countries require the use of the MMSE, and even in Italy there is not a need for improvements in the MMSE but only stabilisation at 3 months.

1.b Other sources of evidence

Hollingworth and Byrne[3] examined trends in the prescribing of subsidised and unsubsidised cognition enhancing drugs (CEDs) in Australia over five years from 2002 to 2007. Because EBIXA was PBS listed on the 1st July 2008, memantine use during the study period represents unsubsidised use only. Such use is not subject to the PBS Mini Mental State Examination (MMSE) initiation and continuation criteria and attracts a higher patient out of pocket expense; hence, unsubsidised use may not be reflective of subsidised use. In contrast to the review prepared for the DUSC, the authors concluded that despite subsidised access to CEDs in Australia, only a minority of people with AD was prescribed these drugs during the period of the study. The authors state that the labyrinth PBS prescribing rules appear to have been effective at limiting access to CEDs, and comment that the relatively low proportion of potentially eligible AD patients dispensed CEDs raises questions for patients, prescribers and government.

PBS prescribing rules for EBIXA stipulate the application for initial and continuing prescription at six months be made in writing. Table 1 demonstrates that of the 17 European countries listed, only three (Belgium,

Finland and The Netherlands) require a written application for the initial prescription, and only one (Belgium) requires a written application for continued supply. None of the seventeen countries requires an improvement in function in order to obtain ongoing reimbursed supply.

The authors' conclusion is confirmed by anecdotal reporting from the network of Lundbeck Australia sales representatives who often receive feedback from general practitioners and specialist prescribers regarding the restrictive nature of the administrative burden associated with access to PBS listed dementia therapies.

2. Whether the two point improvement in MMSE continues to be an adequate surrogate for measuring improvement in patients with dementia treated with these medicines; and are there other more reliable measures of patient-relevant outcomes?

Regarding the 2-point improvement in MMSE required for continuation beyond the sixth prescription, the review prepared for DUSC[1] suggests that prescribers' view of improvement may be more subjective, with prescribers seeking continued subsidy in the event of stabilisation of disease and/or improvement. The possibility of prescribers being strongly influenced by carers' views and concerns about their family members is also raised. Whilst this may be of concern to DUSC, it appears to be consistent with international best practice guidelines such as those issued in the United Kingdom by NICE[8], and reimbursement rules for EBIXA in many European counties (see Table 1).

Also it is important to note that there is no single measure of cognition, function or behaviour that accurately characterises the disease severity stage in each patient. Staging disease severity also considers the impact on family and caregivers and change from premorbid levels[13].

The MMSE has well known limitations, such as failure to take account of level of education, literacy, low English proficiency, and visual problems [4-7]. The cost of using the MMSE may also be prohibitive, since it was copyrighted.

Using improvement in MMSE as the only measure for improvement in order to determine a patient's eligibility to continue therapy purely looks at one domain- cognition. This is not in accordance with international clinical practice guidelines, such as those issued by NICE in the United Kingdom. The relevant NICE guidelines[8] state it is appropriate that treatment be continued only when it is considered to be having a worthwhile effect on cognition, global, functional or behavioural symptoms. The NICE guidelines conclude further that carers' views on the patient's condition at follow-up should be

sought. A consensus statement from the British Association for Psychopharmacology[9] discusses clinically meaningful outcome measures, stating that it should not be underestimated that small symptomatic benefits also matter a great deal to patients and families facing a long and relentless neurodegenerative disease.

Behavioural symptoms such as aggression, agitation and psychosis are common in the moderate to severe stages of AD, and represent an aspect of disease burden that is physically, emotionally and economically challenging, and correlates with early transfer to institutional care[10]. Gauthier *et al* conducted a meta-analysis of six randomised, placebo-controlled , double blind studies which showed that memantine is effective in treating and preventing behavioural symptoms of moderate to severe AD[10]. Specific persistent benefits were observed on the symptoms of delusions and agitation/aggression, which are known to be associated with increased caregiver burden, early institutionalisation, and increased costs of care. Behavioural symptoms were rated using the Neuropsychiatric Inventory (NPI), a rating scale which is copyrighted. The PBAC Public Summary Document for Ebixa[11] reflects the PBAC's view that in the context of moderately severe AD compared to mild disease, that greater weight should be attributed to the non-cognitive domains. Despite this view, improvement in cognition is required to fulfil PBS continuation criteria for EBIXA.

The review prepared for DUSC compares response rates to those observed in clinical studies; however, it is important to note that MMSE data were not included in most memantine clinical trials due to the lack of sensitivity of the MMSE in more severe AD.

Discontinuation after six months of therapy may also occur for reasons other than lack of response. This would be the case for example if a patient initiated therapy in a hospital environment or by another clinician, and the current clinician has no access to baseline MMSE scores due to privacy laws.

An alternative instrument to the MMSE must not only be validated and reliable, it must also be practical and an instrument that clinicians are willing

to use. Alternatively, Australia could adopt the practices of other European countries as outlined in Table 1.

3. If there is more recent evidence on the safety and efficacy of these medicines what would inform the PBAC about their cost-effectiveness

Since the PBS-listing of memantine in Australia, new cost-effectiveness evidence of memantine has been generated. In comparison with previously submitted health economic evidence, cost-effectiveness models for the UK and Norway include additional clinical evidence from clinical trials and more specifically those for adjunct therapy. In these models, the impact on cost-effectiveness of treatment effect on behaviour has been further investigated. Additionally, a cost-effectiveness analysis has been conducted based on real life data[16]. The economic evidence generated on more recent evidence of the safety and efficacy of memantine allowed the drug to be successfully recommended in HTA countries such as the UK and in Norway.

In March 2011 NICE issued a MTA for donepezil, galantamine, rivastigmine and memantine for the Treatment of Alzheimer's Disease[8]. Relevant health clinical and economic evidence has been reviewed by an Appraisal Committee to make a judgment on whether or not the technologies under consideration should be recommended as an effective use of NHS resources. NICE concluded that memantine is to be used as a treatment option for people with moderate AD who are intolerant of or have a contraindication to CEIs and for people with severe AD. The conclusion of the cost-effectiveness evidence of memantine has ensured that patients in England and Wales get access to a clinically effective medication which represents the most efficient use of NHS resources. Memantine was shown to be:

• The dominant treatment option in moderate AD compared to best supportive care;

• A cost-effective treatment option in severe AD compared to best supportive care (ICER of £26,500 and therefore below the £30,000 NICE threshold).

Based on the same economic evidence, the Norwegian Medicines Agency (the NMA) concluded that memantine was cost-effective for patients with severe Alzheimer's dementia, patients with moderate Alzheimer's dementia who have tried CEIs with no effect or who are intolerant to CEIs, and in patients in whom CEIs are contraindicated[15]. This also applied to the subgroup with behavioural disorders. The NMA therefore found that memantine met the medical criteria for inclusion on the list of reimbursable drugs for the full indication.

Both publications of the cost-effectiveness of memantine in Norway and the UK versus standard of care demonstrated that memantine delays the need for full time care and decreases costs.

In 2010, Rive *et al* published a cost-utility analysis of memantine in moderate to severe AD in the United Kingdom which compared memantine to its alternative of no pharmacological treatment or background therapy with CEIs[12]. The authors concluded that memantine delays the need for full time care and decreases costs; hence it can be considered a cost-effective choice in the management of moderate and severe AD.

A study conducted in Norway, assessing the cost-effectiveness of memantine in moderate AD, demonstrated that memantine was found to delay the need for full-time care by 4.4 weeks compared with standard care, and was associated with increased quality of life years[14].

Finally the cost-effectiveness of memantine was assessed using data from an observational study[16] . The study aimed to evaluate the economic impact of the concomitant use of memantine and a CEI, compared with a CEI alone, in a Canadian population of patients with AD. The authors concluded that institutionalisation was the largest cost component in AD management and that the use of memantine, combined with a CEI, to treat AD is a cost-

effective alternative (gain of 0.26 quality-adjusted life years with the treatment including memantine and cost decreases of Can$21 391 and Can$30 512, respectively, for the societal and health care system perspective), compared with the use of a CEI alone[17].

Any review of the cost-effectiveness of memantine in the Australian setting necessitates consideration of the following points:

- the 12.5% statutory price reduction effective 1 August 2010;
- expanded and accelerated price disclosure;
- the increasing cost of institutionalisation;
- the administrative burden for prescribers, pharmacists and Medicare Australia associated with PBS prescribing rules

List of Abbreviations

AD	Alzheimer's disease
ADL	activities of daily living
CED	Cognition enhancing drug
CEI	Choline esterase inhibitor
CIBIC	Clinicians Interview Based Impression of Change
CT	Computed tomography
DUSC	Drug utilisation subcommittee
GP	General practitioner
MMSE	Mini mental state examination
NICE	National Institute of Clinical Excellence
NPI	Neuropsychiatric Inventory
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical benefits schedule

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Table 1 Australia and European requirements for EBIXA reimbursement*

Country	Initial treatment criteria				Continuation criteria		
	Baseline MMSE score	Requirement for specialist to prescribe/ confirm diagnosis	Requirement for written application	Other requirements	Continuation criteria based on improvement in MMSE	Specific continuation criteria	Requirement for written application
Australia	10-14[1]	✓	✓	Sole PBS-subsidised therapy only.	✓	2 point improvement in MMSE at 6 months[2]	✓
Austria	3-14	✓	×[3]	Presence of caregiver to ensure compliance	×	Six monthly clinical review MMSE must remain ≥3	×[3]
Belgium	10-15	✓	✓	Initial diagnosis also with ADL (Katz), ADL (Lawton), GDS, NPI-Q, CGI-C	×	MMSE must remain ≥10	✓
Czech Republic	6-19	✓	×	×	×	Clinical review at 3, 6 ,9 months. MMSE cannot decrease more than 2 points compared to previous	×
Denmark	No requirement	✓	×	Other types of dementia ruled out by CT scan	×	Clinical review at 15 months when GP must document therapeutic effect. No specific requirements for use of diagnostic tools	×
Finland	No requirement	✓	✓	×	×	None	×
France	3-20	✓	×	×	×	None	×
Germany	No requirement	×	×	×	×	Clinical review after at least 24 weeks when a GP or specialist must document therapeutic effect, No specific requirements for use of diagnostic tools	×
Hungary	<20	✓	×	Dementia centres only	×	None Monitoring of treatment effect not required	×
Ireland	No requirement	×	×	×	×	None Monitoring of treatment effect not required	×
Italy	10-20	✓	×	Dementia centres only	×	Stabilisation of MMSE at 3 months Clinical monitoring 6 monthly thereafter	×
Netherlands	<10	✓	✓	×	×	Clinical monitoring at 6 months based	×

						on MMSE & ADL; assessment of effectiveness at prescriber's discretion	
Portugal	No requirement	✓	×	×	×	Ongoing specialist monitoring required	×
Slovakia	8-17	✓	×[3]	Baseline assessment of global function, ADL, behaviour	×	Monitoring by specialist of treatment effect 3 monthly by MMSE, ADL, global functioning, behaviour	×[3]
Slovenia	<20	✓	×	×	×	6 monthly MMSE monitoring required; assessment of effectiveness at prescriber's discretion	×[3]
Spain	<20	✓	×	Diagnosis at hospital level	×	Specialist monitoring required; yearly verification by regional inspection services confirming correct use of product	×
Sweden	No requirement	×	×	×	×	None	×
United Kingdom	No requirement	×	×	×	×	None	×

* EBIXA (memantine) is not reimbursed in Bulgaria, Malta, Poland and Latvia.

[1] MMSE ≤9 allowed for patients unable to register a score of 10-14 for reasons other than AD

[2.] for baseline MMSE was <9: "very much improved" or "much improved" on the CIBIC scale

[3] random prescription monitoring carried out