PUBLIC SUMMARY DOCUMENT

Product: Memantine hydrochloride, tablet, 10 mg and oral solution, 10 mg per mL, Ebixa®

Sponsor: Lundbeck Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The resubmission sought listing as an Authority required benefit for the treatment of moderately severe Alzheimer's disease.

2. Background

This was the fifth submission for memantine. The first submission was to the September 2002 PBAC for treatment of moderately severe to severe Alzheimer's disease (AD), however, this was withdrawn as the ADEC proposed rejection of the product and the issues were not resolved by the PBAC meeting. This submission was therefore not considered by the PBAC.

The PBAC did not accept the cost-minimisation claim compared with donepezil in moderate AD because of the issues relating to the uncertainty surrounding the comparison between the effects of memantine versus donepezil. There was also no basis to make a confident determination of equi-effective doses for pricing purposes.

A resubmission to the November 2004 meeting sought an Authority required listing for initial and continued treatment of moderately severe to severe Alzheimer's disease in patients who were not bedridden and/or mute. The PBAC rejected the application because the extent of effectiveness demonstrated with the drug was of doubtful clinical importance and the resulting uncertain but unfavourable cost-effectiveness.

3. Registration Status

Memantine is registered for the treatment of the symptoms of moderately severe to severe Alzheimer's disease.

4. Listing Requested and PBAC's View

The requested listing for memantine has similar Authority requirements to the anti-cholinesterase inhibitors but with the requirement that the baseline (Standardised) Mini Mental State Examination ((S)MMSE) score must be 10-14.

See Recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Memantine is intended as an alternative treatment to donepezil, galantamine and rivastigmine for the treatment of patients with moderate to severe Alzheimer's disease.

6. Comparator

The submission nominated donepezil as the main comparator as it is the most frequently prescribed anticholinesterase on the PBS. This was considered appropriate by the PBAC.

7. Clinical Trials

The scientific basis of comparison was an indirect comparison of the following trials:

- Memantine vs. placebo: Four trials (previously presented): 99679, MD-01, MD-10, 9605 (24-28 wks) + subgroup analysis (MMSE 10-14)
- Donepezil vs. placebo: one RCT subgroup (Gauthier et al 2002) at 24 weeks

The pivotal trials' citations at the time of the submission are tabulated below.

Trial	Publication title/Publication citation
MEM-MD-01	Forest-Laboratories-Inc. 2005. A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate-to-Severe Dementia of the Alzheimer's Type. http://www forestclinicaltrials com.
MRZ-9605	Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ, Memantine S. 2003. Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine 348:1333-1341. Reisberg B, Ferris S, Sahin K, Windscheif U, Möbius H. 2000. Results of a placebo-controlled 6-month trial with memantine in moderate to severe alzheimer's disease (ad). Journal of the European College of Neuropsychopharmacology 10:S363. Reisberg B, Windscheif U, Ferris SH, Hingorani VN, Stoeffler-Moebius HJ. 2000. Memantine in moderately severe to severe Alzheimer's disease (AD): results of a placebo-controlled 6-month trial. Proceedings of the World Alzheimer Congress ; 2000 Jul 9 13, Washington , DC. Reisberg B, Windscheif U, Ferris SH, Stoeffler A, Moebius HJ, The-Memantine-Study-Group. 2000. Treatment of advanced alzheimer's disease with memantine, an NMDA antagonist: results of a 6-month multicenter randomized controlled trial. 39th Annual Meeting of the American College of Neuropsychopharmacology 2000 ; Dec 10 14; San Juan ; Puerto Rico. Rive B, Vercelletto M, Damier FD, Cochran J, Francois C. 2004. Memantine enhances autonomy in moderate to severe Alzheimer's disease. International Journal of Geriatric Psychiatry. Reisberg B, Stoeffler A, Ferris SH, Schmitt F, Doody RS. 2002. A placebo-controlled study of memantine in advanced alzheimer's disease. 155th Annual Meeting of the American Psychiatric Association; 2002 May 18 23rd ; Philadelphia, PA, USA. Möbius HJ, Stöffler A, Wirth Y, Gauthier S, Merz P, Frankfurt/Main, Germany. 2004. Memantine Positively Influences Behaviour in Moderate to Severe Alzheimer's Disease. Neurobiology of aging 25:19. Feldman H, Schmitt FA, Doraiswamy PM, Graham SM, Bell JM. 2005. Memantine and Individual Activities of Daily Living in Moderate to Severe Alzheimer's Disease. 57th Annual Meeting of the American Academy of Neurology, Miami Beach , April

Trial	Publication title/Publication citation
	2005. Ferris S. 1999. Clinical trial of memantine in severe AD: rationale and design. Proceedings of the 9th Congress of the International Psychogeriatric Association; 1999 Aug 15 20, Vancouver , Canada25. Galasko D, Reisberg B, Mobius HJ, Stoffler A. 2003. Functional improvement from treatment with the NMDA antagonist memantine: results of a 28 week, randomized, placebo-controlled study in moderate to severe Alzheimer's disease. Poster at teh 6th International Conference AD /PD 2003 May 8 12, 2003 Seville, Spain. Moebius HJ, Wirth Y, Gauthier S. 2005. Memantine: Behavioral Benefits for Moderate to Severe Alzheimer's Patients. 57th Annual Meeting of the American Academy of Neurology, Miami Beach , April 2005.
MEM-MD-10	Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, McDonald S. 2006. Memantine treatment in mild to moderate Alzheimer disease: A 24-week randomized, controlled trial. American Journal of Geriatric Psychiatry 14(8):704-715. Potkin SG, McDonald S, Gergel I, Alva G, Keator DB, Fallon JH. 2004. Memantine monotherapy increases brain metabolism (PET) and effectively treats mild to moderate Alzheimer's disease. 8th Congress of the European Federation of the Neurological Sciences Paris, France September 4 7, 2004. Cummings JL, Schneider E, Peskind ER, Tariot PN, Graham SM, Bell JM. 2005. Effect of Memantine on Behavioral Outcomes in Mild to Severe Alzheimer's Disease. 57th Annual Meeting of the American Academy of Neurology, Miami Beach , April 2005. Pomara N, Peskind ER, Potkin SG, McDonald S, Xie Y, Gergel I, New-York-University-School-of-Medicine, New Y, NY, USA. 2004. Memantine Monotherapy is Effective and Safe for the Treatment of Mild to Moderate Alzheimer's Disease: A Randomized Controlled Trial. Neurobiology of aging 25:19.
Gauthier S et al	Donepezil MSAD. 2002. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. Current Medical Research & Opinion 18:347-354.

8. Results of Trials

The key results are summarised in the table below:

Comparison	Sub-population	Odds Ratio (95% CI)	P-value
CIBIC Plus – patients with no change, or improvement			
Memantine vs. Donepezil	10-17 vs. 10-17	0.59 (0.28, 1.26)	0.171
	10-14 vs. 10-17	0.64 (0.22, 1.84)	0.405
CIBIC Plus – score at endpoint		**WMD (95% CI)**	
Memantine vs. Donepezil	10-17 vs. 10-17	0.27 (–0.10, 0.64)	0.151
	10-14 vs. 10-17	0.01 (–0.39, 0.42)	0.955
NPI – change from baseline			
Memantine vs. Donepezil	10-17 vs. 10-17	4.02 (–1.27, 9.32)	0.136
	10-14 vs. 10-17	4.29 (-0.44, 9.01)	0.076
SIB – change from baseline			
Memantine vs. Donepezil	10-17 vs. 10-17	–0.33 (–9.58, 8.93)	0.944
	10-14 vs. 10-17	-0.36 (-9.80, 9.08)	0.940

CIBIC-plus - Clinician's Interview-Based Impression of Change (incorporating caregiver information; by design the baseline score, 'no change' is set at 4.00 and range is 1-7)
NPI- Neuropsychiatric Inventory (are from the patient assessments; score range 0-120)

SIB - Severe Impairment Battery (Cognitive domain - score range 0-100)

The PBAC noted that although there are no significant differences between memantine and donepezil, the possibility of Type II error for this comparison had not been addressed (the power of the individual studies had been addressed, but not of the comparison between the two studies). In general, the results for donepezil vs. placebo were consistently larger in most of the measures (except SIB). In addition, the comparison for NPI was close to reaching statistical significance.

There was no data to show that memantine improves MMSE. The submission provided data from study 9605 that failed to show any clinically relevant increase in MMSE either in the whole sample or in the subgroup 10-14. The change from baseline MMSE in patients treated with memantine was 0.11. Previously the PBAC had considered a change from baseline of 2 points to be the clinically important difference in AD.

MMSE outcome results for trial 9605

	Treatment	ITT (n=126)	MMSE 10-14/10-17 § (n=45)
Baseline	Memantine	7.72±3.72	11.29±2.36
	Placebo	8.05±3.57	11.18±2.08
Endpoint (28w)	Memantine	7.21±4.69	11.40±3.42
	Placebo	6.90±4.34	9.86±4.32
Change from baseline	Memantine	-0.52±2.38	0.11±2.42
	Placebo	-1.14±3.00	-1.33±3.72

§ The patient population for MMSE 10-14 was the same as for MMSE 10-17.

The re-submission presented new toxicity data for the acetylcholinesterase comparators vs. placebo, showing that there were more adverse events associated with acetylcholinesterase inhibitors than with memantine.

9. Clinical Claim

The submission claimed that memantine is no worse than donepezil in terms of effectiveness and toxicity.

The PBAC noted the use of memantine is associated with fewer adverse events than use of the acetylcholinesterase inhibitors. However, the PBAC considered that it could not be concluded that memantine is no worse than donepezil in terms of effectiveness.

For further details see under Recommendation and Reasons.

10. Economic Analysis

An updated preliminary economic evaluation was presented which consisted of a cost-minimisation analysis against donepezil.

A modelled economic evaluation was not presented. This was appropriate.

11. Estimated PBS Usage and Financial Implications

The likely number of scripts per year was estimated to be between 10,000 and 50,000 per year. The financial cost per year to the PBS was estimated to be less than $10 million per year.

12. Recommendation and Reasons

The PBAC noted that listing was sought for the treatment of moderately severe Alzheimer's disease in patients who have a baseline Mini-Mental State Examination (MMSE) or SMMSE (standardised MMSE) of 10-14 and considered the submission did not provide sufficiently comprehensive Mini-Mental State Examination (MMSE) data for memantine. The MMSE was not a primary or secondary outcome measure in the four memantine trials included in the submission. Although the submission provided baseline MMSE scores for these trials, they could not be independently verified. The PBAC noted the Pre-PBAC Response regarding the lack of comprehensive MMSE data, and while, accepting that the MMSE may not be the appropriate measure for *severe* Alzheimer's disease, did not consider the response adequately addressed this situation where the requested listing was for moderately severe Alzheimer's disease, particularly as patients are required to achieve an improvement of two points on the MMSE scale to qualify for the first continuing therapy.

The PBAC considered the re-submission had been selective in the trials excluded. For example, the memantine 9403 trial was excluded because it was the 'wrong AD severity'; however the patients were moderately severe to severe AD (consistent with the current re-submission). Some of the donepezil trials (Mohs 2001, Tariot 2001 and Winblad 2001) were excluded from the current re-submission as they were all the 'wrong AD severity'. However, the inclusion criteria for the trials and baseline characteristics were similar to the sole included donepezil trial (Gauthier et al). Therefore, notwithstanding the statistical results indicating that there is no statistically significant difference between memantine and donepezil (from an indirect comparison involving placebo as the common reference), the mean data suggested that memantine may have a numerically smaller effect overall. Further, no evidence was provided to demonstrate that memantine can increase the MMSE score by 2 points. Potentially useful information would be the proportions of patients in each arm (i.e. both memantine and placebo arms) of the memantine trials who reported an increase in the MMSE score by 2 points, because this would enable a prediction of who would thus be eligible for continuing therapy according to the requested restriction in the submission.

The PBAC also noted that in general, the trial results presented for donepezil vs. placebo were consistently more favourable in most of the measures (except Severe Impairment Battery) than the corresponding results for memantine vs. placebo. In addition, the results of the indirect comparison of donepezil vs. memantine for Neuropsychiatric Inventory (NPI) were close to reaching a statistically significant difference favouring donepezil.

The conclusion in the recent NICE guidance (November 2006) on the use of donepezil, galantamine, rivastigmine and memantine for the treatment of mild to moderately severe Alzheimer's disease that memantine is not recommended as a treatment option for people with moderately severe to severe disease except as part of well designed clinical studies was noted.

The PBAC noted the use of memantine is associated with fewer adverse events than use of the acetylcholinesterase inhibitors. However, the PBAC considered that it could not be concluded that memantine is no worse than donepezil in terms of effectiveness. The Committee therefore rejected the submission for listing on a cost-minimisation basis compared to donepezil.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Lundbeck is disappointed with the outcome and remains committed to ensuring that Australians with Alzheimer's disease have access memantine. We are working with the PBAC to resolve the issues and gain PBS listing of memantine.