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 2008

1. Purpose of Application
The re-submission sought listing an Authority Required benefit for the treatment of moderately severe Alzheimer's disease (AD).

2. Background
Memantine has been considered several times previously by the PBAC.

At the most recent consideration in March 2007 meeting, the PBAC rejected the submission for listing on a cost-minimisation basis compared to donepezil. The PBAC noted that listing was sought for the treatment of moderately severe AD in patients who have a baseline (Standardised) Mini-Mental State Examination ((S)MMSE) score 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.

3. Registration Status
Memantine was TGA registered on 17 April 2003 for 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.

For the complete restriction, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy
Memantine would provide an alternative treatment to donepezil, galantamine and rivastigmine for the treatment of patients with moderately severe Alzheimer's disease.

6. Comparator
The re-submission nominated donepezil, galantamine and rivastigmine as the main comparators.
The PBAC accepted this as appropriate.

7. Clinical Trials
The basis of the re-submission was an indirect meta-analysis of four randomised trials of memantine and 12 donepezil, three galantamine and seven rivastigmine trials with placebo as the common comparator.
The data presented included:
- Memantine – (4 trials): 99679, MD-01, MD-10, 9605 @ 5-20 mg/d (24-28 wks)
- Donepezil – (12 trials) @ 2-10 mg/day (24-27 wks)
- Galantamine – (3 trials) @ 24(32) mg/day (24-26 wks)
- Rivastigmine – (7 trials) @ 2-12 mg/day (and patches) (26 wks)

Studies published at the time of the submission are presented in the table below.

Trial	Publication title/Publication citation
Memantine	
MEM-MD-01	Trial MEM-MD-01: 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. 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.
MEM-MD-10	Trial MEM-MD-10: A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with mild to moderate dementia of the Alzheimer's type. 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.
MRZ-9605	Trial MRZ-9605: Efficacy and long-term tolerability of memantine in patients with moderately severe to severe Alzheimer's disease (AD). 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. 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. 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. 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 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 , Canada. 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 the 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.
Donepezil	
Burns (1999)	Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, Rogers SL, Friedhoff LT. 1999. The effects of donepezil in Alzheimer's disease - results from a multinational trial. Dementia & Geriatric Cognitive Disorders 10:237-244. Gauthier S, Rossor M, Hecker J, Burns A, Petite H, Moeller HJ, Regers SL, Friedhoff LT. 1998. Results from a multinational phase III clinical trial of donepezil in Alzheimer's disease. Proceedings of the 5th International Springfield Symposium on Advances in Alzheimer Therapy; 1998 , Apr 15 18, Geneva.

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Feldman (2001)	Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, Donepezil MSAD. 2001. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease.[erratum appears in Neurology 2001 Dec 11;57(11):2153]. Neurology 57:613-620. Feldman H, Gauthier S, Hecker J, Vellas B, Emir B, Mastey V, Subbiah P, Donepezil MSAD. 2003. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden.[see comment][erratum appears in J Am Geriatr Soc. 2003 Sep;51(9):1331]. Journal of the American Geriatrics Society 51:737-744. Gauthier S, Feldman H, Vellas B, Subbiah P. 2000. Efficacy of donepezil on functional, behavioural and cognitive symptoms in patients with moderate to severe Alzheimer's disease. Journal of the American Geriatrics Society 48:S2. Gauthier S. 2004. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate-to-severe Alzheimer's disease, and impact on caregiver burden. Geriatrics and Aging 7. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. 2000. Donepezil provides benefits in global function in moderate to severe Alzheimer's Disease. Proceedings of the World Alzheimer Congress ; 2000 Jul 9 13, Washington DC. Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Xu Y, Schwam EM, Shah S, Mastey V, Donepezil MSAD. 2004. Economic evaluation of donepezil in moderate to severe Alzheimer disease.[see comment]. Neurology 63:644-650. Feldman H, Gauthier S, Hecker J, Vellas B, Emir B, Mastey V, Subbiah P. 2002. Donepezil treatment benefits caregivers of patients with moderate to severe Alzheimer's disease (AD). European journal of neurology : the official journal of the European Federation of Neurological Societies 9:34. Subgroup analysis:

	Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P, Donepezil MSAD. 2002. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. Current Medical Research & Opinion 18:347-354. Gauthier S, Feldman H, Hecker J, Vellas B, Ames D, Subbiah P, Whalen E, Emir B, Donepezil MSAD. 2002. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. International Psychogeriatrics 14:389-404. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. 2000. Donepezil's benefits on cognition, global function, activities of daily living and behavior in patients with moderate to severe Alzheimer's disease. Proceedings of the 6th International Stockholm /Springfield Symposium on Advances in Alzheimer Therapy; 2000 Apr 5 8, Stockholm , Sweden174. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, Donepezil-MSAD-Study-Group. 2000. Benefits of Donepezil on global function, behavior, cognition and ADLs in patients with moderate to severe Alzheimer's disease. Neurology 54:A469. Feldman H, Gauthier S, Vellas B, Hecker J, Xu Y, Jeni J, Schwam E. 2003. Donepezil Has Significant Benefits on Behavior in Patients With Severe Alzheimer's Disease. 156th Annual Meeting of the American Psychiatric Association, May 17 22, San Francisco CANR886. Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P. 2002. Exploratory analysis of the effects of donepezil in moderate and severe Alzheimer's disease patients. Proceedings of the 8th International Conference on Alzheimer's Disease and Related Disorders; 2002 July 20 25, Stockholm , SwedenAbstractNo277. Gauthier S, Feldman H, Hecker J, Vellas B, Subbiah P, Whalen E. 2000. Effects of donepezil on behaviour and other domains in moderate to severe Alzheimer's disease. Journal of the European College of Neuropsychopharmacology 10:S359. Gauthier S, Feldman H, Hecker J, Vellas B, Subbiah P, Whalen E. 2000. Benefits of Donepezil on performance of basic and instrumental activities of daily living in moderate to sever Alzheimer's Disease. Proceedings of the World Alzheimer Congress ; 2000 Jul 9 13, Washington DC. Hecker J, Foti D, Gauthier S, Vellas B, Subbiah P, Whalen E. 2000. Benefits of Donepezil in the treatment of behavioural problems in moderate to severe Alzheimer's Disease. Proceedings of the World Alzheimer Congress ; 2000 Jul 9 13, Washington DC. Vellas B, Feldman H, Gauthier S, Hecker J, Subbiah P, Whalen E, Mastey V. 2000. Donepezil treatment in patients with moderate to severe Alzheimer's Disease reduces caregiver stress. Proceedings of

	the World Alzheimer Congress ; 2000 Jul 9 13, Washington, DC. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. 2002. Donepezil improves neuropsychiatric symptoms in moderate to severe Alzheimer's disease. 155th Annual Meeting of the American Psychiatric Association; 2002 May 18 23rd ; Philadelphia, PA, USA. Feldman H, Gauthier S, Hecker J, Vellas B, Xu Y, Ieni JR, Schwam EM, Donepezil MSAD. 2005. Efficacy and safety of donepezil in patients with more severe Alzheimer's disease: a subgroup analysis from a randomized, placebo-controlled trial. International Journal of Geriatric Psychiatry 20:559-569. Feldman H, Gauthier S, Hecker J, Vellas B, Ieni J, Xu Y, Schwam E. 2005. Treatment Benefits of Donepezil in Patients with Severe Alzheimer's Disease and Their Caregivers. 57th Annual Meeting of the American Academy of Neurology, Miami Beach , April 2005.
Homma (1998)	Homma A, Imai Y, Hariguchi S, Hasegawa K, Kameyama M, Nishimura T. 1998. Late Phase II Clinical Study of Acetylcholinesterase Inhibitor E2020 in Patients with Alzheimer-type Dementia -24-48-weeks Double-blind, Placebo-Controlled Study-. Rinsho Hyoka 26:209-231.
Homma (2000)	Homma A, Imai Y, Hariguchi S, Hasegawa K, Kameyama M, Nishimura T. 1998. Late Phase II Clinical Study of Acetylcholinesterase Inhibitor E2020 in Patients with Alzheimer-type Dementia -24-48-weeks Double-blind, Placebo-Controlled Study-. Rinsho Hyoka 26:209-231.
Krishnan (2003)	Krishnan KR, Charles HC, Doraiswamy PM, Mintzer J, Weisler R, Yu X, Perdomo C, Ieni JR, Rogers S. 2003. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. American Journal of Psychiatry 160:2003-2011.
Mazza (2006)	Mazza M, Capuano A, Bria P, Mazza S. 2006. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. European Journal of Neurology 13:981-985.
Moraes (2006)	Moraes W, Poyares DR, Guilleminault C, Ramos LR, Bertolucci PH, Tufik S. 2006. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep 29(2):199-205.
Rogers (1998a)	Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. 1998. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group.[see comment]. Neurology 50:136-145. Rogers SL, Doody R, Mohs R, Friedhoff LT, The-Donepezil-Study-Group. 1996. E2020 produces clinical, global and cognitive test improvement in patients with mild to moderately severe Alzheimer's disease: Results of a 30-week phase III trial. Neurology 46Suppl:217.

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Selzer (2004)	Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S, Donepezil 4S. 2004. Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial.[erratum appears in Arch Neurol. 2005 May;62(5):825]. Archives of Neurology 61:1852-1856. Seltzer B, Zolnouni P, Nunez M, Goldman R, Noble Y, Kumar D, Griesing T, Richardson S. 2002. Donepezil treatment improves cognitive performance in patients with very mild Alzheimer's disease. European Neuropsychopharmacology; 15th International Congress of the European College of Neuropsychopharmacology, October 5 9, Barcelona, Spain 12:S385. Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S. 2005. Erratum: Efficacy of donepezil in early-stage Alzheimer disease: A randomized placebo-controlled trial (Archives of Neurology (December 2004) 61 (1852-1856)). Archives of Neurology 62. Richardson S, Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J. 2003. Donepezil Treatment Benefits Early-Stage Alzheimer's Disease. 156th Annual Meeting of the American Psychiatric Association, May 17 22, San Francisco CANR827.
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Winblad (2006)	Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL, Jansson-Blixt C, Haglund A, Severe A. 2006. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study.[see comment]. Lancet 367:1057-1065.
Galantamine	
Brodaty (2005)	Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M, Damaraju CR. 2005. Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. Dementia & Geriatric Cognitive Disorders #2005. Brodaty H, Yan B, Damaraju CV, Gold M. 2004. Safety and tolerability of once-daily galantamine prolonged-release in patients with mild to moderate Alzheimer's disease. 8th Congress of the European Federation of the Neurological Sciences Paris, France September 4 7, 2004. Corey BJ, Gold M, Yan B, Truyen L, Johnson-&-Johnson-Pharmaceutical-Research-, Titusville, NJ, USA. 2004. The Safety and Efficacy of an Extended-Release Formulation of Galantamine (Reminyl ER) in the Treatment of Alzheimer's Disease. Neurobiology of Aging 25:18.
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Rivastigmine	
Ballard (2005)	Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, O'Brien J, Everratt A, Sadler S, Maddison C, Lee L, Bannister C, Elvish R, Jacoby R. 2005. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial.[see comment]. BMJ 330:874.
Corey-Bloom (1998)	Corey-Bloom J, Anand R, Veach J. 1998. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. International Journal of Geriatric Psychopharmacology 1. Kumar V, Anand R, Messina J, Hartman R, Veach J. 2000. An efficacy and safety analysis of Exelon in Alzheimer's disease patients with concurrent vascular risk factors. European Journal of Neurology 7:159-169. Veach KRRK, SM, Doraiswamy PM. 1999. Rivastigmine slows stage-specific global deterioration in Alzheimer's disease. 152nd Annual Meeting of the American Psychiatric Association Washington DC, USA 15 20th May, 1999.
Feldman (2007)	Feldman HH, Lane R. Rivastigmine: A placebo-controlled trial of BID and TID regimens in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2007 Mar 12. Data obtained from Cochrane review; Birks J. 2006. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews (1):CD005593.
RIV-B351	Data obtained from Cochrane review; Birks J. 2006. Cholinesterase

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Tai (2000)	Tai CT, Liu CK, Sung SM, Pai MC, Hsu CY. 2000. The safety and efficacy of exelon in Alzheimer's patients: a multicentre, randomized, 26-week study in Taiwan. International Journal of Neuropsychopharmacology 3:S356.
Winblad (2007)	Winblad B, Cummings J, Andreasen N, Grossberg G, Onofrj M, Sadowsky C, Zechner S, Nagel J, Lane R. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease-- rivastigmine patch versus capsule. Int J Geriatr Psychiatry. 2007 Mar 22. Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, Nagel J, Lane R (2007), IDEAL: A 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease, Neurology 69: S14-S22.

8. Results of Trials

In general, there was no statistically significant difference in any outcome between memantine and placebo. The only statistically significant differences ($p<0.05$) were Alzheimer's Disease Assessment Scale – cognitive (ADAS-Cog) responder (99769), ADAS-cog (MD-10), and Severe Impairment Battery (SIB), Functional Assessment Staging (FAST), and Alzheimer's Disease Cooperative Study – Activities of Daily Living – change in sum (ADCS-ADL-css) (9605), favouring memantine. There was no significant difference in MMSE score in study 9605.

The individual trial results for donepezil, galantamine and rivastigmine were presented in the submission. There were statistically significant differences in most, but not all, outcomes in favour of donepezil in the donepezil trials, but the effect size again was small (2-3 points on the 70 point ADAS-Cog scale). The placebo response was much greater than the difference between the active and placebo treatment effect sizes. Similar comments apply to galantamine and rivastigmine.

The re-submission grouped the outcomes from the trials into several 'domains' as outlined in the table below.

Outcome measures classified into 'domains'

Domain	Outcome
"GLOBAL" Clinician's global assessment outcome	**Clinician's global impression of change (higher score, greater deficity)**
	Clinical Global Impression of Change scale (CGIC) and the global improvement index with interviewing of patients. Clinician Interview-Based Impression of Change (CIBIC) and with caregiver input (CIBIC-M or –Plus)
	Clinician's global impression of severity (higher score, greater deficity)
	Clinical Dementia Rating (CDR) and Clinical Dementia Rating Sum of Boxes (CDR-SB)
	Global Deterioration Scale (GDS)
	Gottfries-Bråne-Steen (GBS)
	Mental Function Impairment Scale (MENFIS)
"COGNITION" Cognitive function	Alzheimer's Disease Assessment Scale cognitive (ADAS-cog) and ADAS-Jcog
	Mini-Mental State Examination (MMSE)
	Severe Impairment Battery (SIB)
"DISABILITY" Functional outcome measurement	Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS/ADL23)
	Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS/ADL19)
	Behavioural Rating Scale for Geriatric Patients (BGP)
	Disability Assessment for Dementia (DAD)
	Instrumental Activities of Daily Living (IADL)
	Physical Self-Maintenance Scale (PSMS)
	The Progressive Deterioration Scale (PDS)
"BEHAVIOUR" Behavioural outcome	Neuropsychiatric Inventory (NPI)

The table below summarises the main results from the meta-analyses of the randomised trials for the four domains.

Meta-analyses results for the four domains (change from baseline)

Domain	Trials	Mem n	Pbo n	AChEIs n	SMD	Difference (95%CI)	p value
Global	4	311	266		*-0.36 (-0.52, -0.19) F*	0.098 †should be 0.03 (-0.130, ∞)	0.481
	5		785	1080	-0.33 (-0.46, -0.20) R		
Cognition	4	303	264		*-0.32 (-0.57, -0.16) R*	**-0.114** (-0.330, ∞)	0.388
	10		1542	2467	-0.43 (-0.54, -0.31) R		
Disability	4	312	267		*-0.24 (-0.41, -0.08) F*	0.107 (-0.047, ∞)	0.252
	6		941	1640	-0.13 (-0.22, -0.05) F		
Behaviour	4	308	266		*-0.17 (-0.34, -0.01) F*	0.082 (-0.096, ∞)	0.449
	2		355	582	-0.09 (-0.23, 0.04) F		

Notes: F = fixed effects; R = random effects meta-analysis; *† error – difference should be ~0.03;* **Bold =** favours AChEIs; **∞ = a one-sided confidence interval was used for which the upper bound is not informative and results in a bias towards a non-inferiority result.

The PBAC noted that in contrast to the results of the individual trials, which suggested that there are only a few statistically significant differences between memantine and placebo and the effect sizes were small, the grouping of outcomes into domains produced statistically significant differences between memantine and placebo.

The PBAC noted that the results of the meta-analysis must be interpreted with caution, given the poorly justified exclusion of many trials. There were also significant statistical and methodological issues in relation to the meta-analysis itself. A major issue was the definition of a "minimum clinically detectable difference" in the absence of MMSE data. The choice made by the sponsor was a statistical concept rather than a clinical one relevant to Alzheimer disease. A further important methodological issue was the correction of the significance level to account for multiple comparisons. In summary, the method of meta-analysis is subject to significant uncertainty and insufficient detail was provided in the re-submission.

In relation to safety, the PBAC had previously accepted that memantine is better tolerated than AChEIs.

9. Clinical Claim

The submission claimed memantine is non-inferior in terms of comparative effectiveness and "better" in terms of comparative safety over the AChEIs (donepezil, galantamine and rivastigmine).

Based on the evidence presented, the PBAC considered that memantine had a 'better' safety profile but lesser efficacy, associated with some uncertainty, than the anticholinesterases.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as memantine 20 mg/day and donepezil 10 mg/day. This was unchanged from the previous submissions. Given the PBAC's views with respect to the clinical claim, this approach was not accepted as valid. However, the PBAC considered that based on the lower price proposed in the Pre-PBAC Response, listing on the basis of acceptable cost-effectiveness at that price was appropriate.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of packs dispensed as up to between 10,000 and 50,000 in Year 4. The estimated financial cost per year to the PBS was less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of memantine as monotherapy for the treatment of moderately severe Alzheimer's disease on the basis of acceptable cost-effectiveness compared to donepezil, galantamine and rivastigmine.

The PBAC noted limited data were available comparing memantine to the acetylcholinesterase inhibitors (AChEIs) and although MMSE was used to establish the baseline characteristics of the patients enrolled in the four memantine trials, MMSE results are only available for trial 9605. The PBAC also noted that there was selective use of trials in the re-submission compared to previous submissions. The PBAC was advised that given the issues of trial selection, and the use of "lumped" endpoints, the evidence to support non-inferiority remains very uncertain.

The PBAC noted the Pre-Sub-Committee response stated that "although MMSE data were not included in memantine trials due to the lack of reliability in more severe Alzheimer's

disease, this should not preclude the use of MMSE for initiation and continuation of memantine for moderately severe Alzheimer's disease." The Committee agreed that MMSE remained an appropriate means of determining eligibility for initial and continuing treatment for the anti-dementia drugs.

With respect to the trial data presented the PBAC noted that in the memantine studies versus placebo, in general there were no statistically significant differences in most of the outcomes between treatments. The only statistically significant differences ($p<0.05$) were ADAS-Cog responder (99769), ADAS-cog (MD-10), and SIB (Severe Impairment Battery), FAST (Functional Assessment Staging), ADCS-ADL-css (9605), favouring memantine. There was however, no significant difference in MMSE score in study 9605. For donepezil, galantamine and rivastigmine, in trials versus placebo there were statistically significance differences in most, but not all outcomes, favouring the active arms.

The PBAC also noted that in contrast to the results of the individual trials, which suggested that there were only a few statistically significant differences between memantine and placebo and the effect sizes were small, the grouping of outcomes into domains (global, cognition, disability, behaviour) produced statistically significant differences between memantine and placebo and no significant differences between memantine and the AChEIs, except on the "cognition domain". The PBAC considered the results of the meta-analysis must be interpreted with caution, given the poorly justified exclusion of many trials. There were also some statistical and methodological issues in relation to the meta-analysis itself.

Overall, the PBAC considered that in the context of moderately severe Alzheimer's disease compared to mild disease that greater weight that could be attributed to the non-cognitive domains and a recommendation to list memantine as an additional treatment option for the treatment of moderately severe Alzheimer's disease on the basis of a 'better' safety profile but lesser efficacy associated with some uncertainty compared with the AChEIs, was acceptable.

Recommendation

MEMANTINE HYDROCHLORIDE, tablet, 10 mg, and oral solution, 10 mg per mL, 50 mL.

Restriction: <u>Authority required</u>

INITIAL APPLICATION FOR THE TREATMENT OF MODERATELY SEVERE ALZHEIMER'S DISEASE — Patients with an (S)MMSE of 10-14.

Initial treatment, as the sole PBS-subsidised therapy, of moderately severe Alzheimer's disease. Confirmation of this diagnosis must be made by a specialist/consultant physician (including a psychiatrist). The authority application must include the result of the baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE). This baseline (S)MMSE must be a score of 10 -14;

This application must be made in writing, but initial supply may be sought by telephone.

For telephone applications, up to a maximum of 2 months' initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment.

For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats will be authorised.

CONTINUING TREATMENT — (S)MMSE
Continuing treatment, as the sole PBS-subsidised therapy, following initial PBS-subsidised therapy, of moderately severe Alzheimer's disease in patients with demonstrated improvement in cognitive function as measured by an increase of at least 2 points from baseline on the Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE);

The initial authority application for continuing treatment must include the relevant result from the (S)MMSE and must be in writing. Subsequent applications for continuing treatment can be made by telephone.

Authority required
INITIAL APPLICATION FOR THE TREATMENT OF MODERATELY SEVERE ALZHEIMER'S DISEASE — Patients with an (S)MMSE of 9 or less who require a clinician's assessment. Initial treatment, as the sole PBS-subsidised therapy, of moderately severe Alzheimer's disease of patients with a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 9 or less, who are unable to register a score of 10-14 for reasons other than their Alzheimer's disease, as specified below. Confirmation of this diagnosis must be made by a specialist/consultant physician (including a psychiatrist).
Such patients will need to be assessed using the Clinicians Interview Based Impression of Severity (CIBIS) scale. The authority application must include the result of the baseline (S)MMSE and specify to which group(s) (see below) the patient belongs.
This application must be made in writing, but initial supply may be sought by telephone.
For telephone applications, up to a maximum of 2 months' initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment.
For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats will be authorised.

Patients who qualify under this criterion are from 1 or more of the following groups:
(1) Unable to communicate adequately because of lack of competence in English, in people of non-English speaking background;
(2) Limited education, as defined by less than 6 years of education, or who are illiterate or innumerate;
(3) Aboriginal or Torres Strait Islanders who, by virtue of cultural factors, are unable to complete an (S)MMSE test;
(4) Intellectual (developmental or acquired) disability, eg Down's syndrome;
(5) Significant sensory impairment despite best correction, which precludes completion of an (S)MMSE test;
(6) Prominent dysphasia, out of proportion to other cognitive and functional impairment.

CONTINUING TREATMENT — Clinician assessed improvement.
Continuing treatment, as the sole PBS-subsidised therapy, following initial PBS-subsidised therapy, of moderately severe Alzheimer's disease in patients with demonstrated improvement in function, based on a rating of "very much improved" or "much improved" on the Clinicians Interview Based Impression of Change (CIBIC) scale, which must be assessed by the same clinician who initiated treatment.

The initial authority application for continuing treatment must state the improvement achieved on the CIBIC scale and must be in writing. Subsequent applications for continuing treatment can be made by telephone.

Authority required
APPLICATION FOR THE TREATMENT OF MODERATELY SEVERE ALZHEIMER'S DISEASE — Patients who commenced treatment prior to 1 March 2008.
Continuing treatment, as the sole PBS-subsidised therapy, of a patient commenced on memantine prior to 1 March 2008.

Applications for continuing treatment can be made by telephone.

Maximum quantity:	56 (tablet), 1 (oral solution)
Repeats:	5 (both forms)

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 Australia welcomes the PBAC's decision to recommend Ebixa for listing on the PBS for the treatment of moderately severe Alzheimer's disease. However, the Sponsor contends that Ebixa is equivalent to the acetylcholinesterase inhibitors in this spectrum of the Alzheimer's disease population.