PUBLIC SUMMARY DOCUMENT
Product: Zonisamide, capsule, 25, 50 and 100 mg, Zonegran®
Sponsor: Eisai Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application
To seek an Authority required listing for the treatment of epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs.

2. Background
This drug has not previously been considered by the PBAC.

3. Registration Status
Zonisamide was TGA registered on 31 July 2007 as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

4. Listing Requested and PBAC's View
Authority Required
Treatment of epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Zonisamide will provide an alternative treatment option to lamotrigine (in partial seizures), gabapentin, vigabatrin, topiramate and levetiracetam.

6. Comparator
The submission nominated lamotrigine as the main comparator. The PBAC considered this was appropriate.

7. Clinical Trials
The submission presented an indirect comparison of zonisamide (meta-analysis of four trials) with lamotrigine (meta-analysis of nine trials) in epileptic patients.

The trials published at the time of submission were as follows:

Trial ID/First author	Protocol title	Publication citation
Zonisamide		
302 Brodie MJ et al	Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures.	Epilepsia. 2005; 46(1):31-41.
922 Faught E et al	Zonisamide 922 Trial Group. Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures.	Neurology. 2001; 57(10):1774-9.
Brodie MJ 912-EUR	Zonisamide clinical trials: European experience.	Seizure. 13 Suppl 1:S66-70 discussion S71-2, 2004 Dec.

Trial ID/First author	Protocol title	Publication citation
Schmidt D	Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial.	Epilepsy Research. 1993;15(1):67-73.
Sackellares JC et al (912-US)	Randomized, controlled clinical trial of zonisamide as adjunctive treatment for refractory partial seizures.	Epilepsia. 2004 Jun;45(6):610-7
Lamotrigine		
Binnie 1989	Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy.	Epilepsy Research 1989 4:222-9.
Boas 1996	Controlled trial of lamotrigine (Lamictal) for treatment - resistant partial seizures.	Acta Neurologica Scandinavica 1996 94:247-52.
Jawad 1989	Controlled trial of lamotrigine (Lamictal) for refractory partial seizures.	Epilepsia 1989 30(3):356-63.
Loiseau 1990	A randomised double-blind placebo -controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures.	Epilepsy Research 1990 7:136-45.
Matsuo 1993	Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures.	Journal of Neurology 1993 43:2284-91
Messenheimer 1994	A multicenter, placebo-controlled, double-blind, cross-over trial.	Epilepsia 1994 35(1):113-21.
Schachter 1995	A six-month, placebo-controlled, safety and tolerance study.	Journal of Epilepsy 1995 8:201-9.
Schapel 1993	Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures.	Journal of Neurol-ogy, Neurosurgery, & Psychiatry 1993 56:448-53.
Smith 1993	Outcomes of add-on treatment with lamotrigine in partial epilepsy.	Epilepsia 1993 34(2):312-22.

8. Results of Trials

Results of key trials (≥50% reduction in seizure frequency)

Trial ID	Risk difference (95%CI)	Zonis § n/N (%)	Pbo n/N (%)	Lamot n/N (%)	Risk difference (95%CI)
Zonisamide trials					
(302) 100mg 300mg 500mg	0.25 (0.15, 0.35) [b]	17/55 (30.9) 19/55 (34.5) 55/118 (46.6)	21/119 (17.6)		

922	0.21 (0.07,0.34)	42/98 (42.9)	16/72 (22.2)		
912US	0.13 (0.00,0.27)	20/69 (29.0)	11/71 (15.5)		
912EUR	0.18 (0.04,0.31)	20/67 (29.9)	8/66 (12.1)		
Lamotrigine trials					
Binnie 1989			1/18 (5.5)	1/16 (6.3)	0.01 (-0.15, 0.17)
Boas 1996			4/26 (15.4)	6/30 (20)	0.05 (-0.15, 0.25)
Jawad 1989			1/12 (8.3)	6/12 (50)	0.42 (0.09, 0.74)
Loiseau 1990			1/14 (7.1)	2/11 (18.2)	0.11 (-0.15, 0.38)
Matsuo 1993			10/73 (13.7)	33/143 (23.1)	0.09 (-0.01, 0.20)
Mess'mer 94			4/52 (7.7)	10/46 (21.7)	0.14 (0.00, 0.28)
Schachter 95			NA	NA	NA
Schapel 1993			1/21 (4.8)	5/20 (25)	0.20 (-0.01, 0.41)
Smith 1993			1/40 (2.5)	4/41 (9.8)	0.07 (-0.03, 0.18)
Zonisamide pooled	0.20 (0.14, 0.26)	156/407 (38)	56/328(17)		
Chi-square heterogeneity	P=0.57				
I^2 statistic	0%				
Lamotrigine pooled			23/256 (9)	67/319 (21)	**0.10 (0.04, 0.15)**
Chi-square heterogeneity					P=0.42
I^2 statistic					0.7%
Indirect comparison of zonisamide and lamotrigine (random effects)					
Risk difference	0.10 (0.02, 0.18)				
Risk ratio	1.05 (0.62, 1.76)				

b only 300mg and 500mg zonisamide combined
§ outcome was available for the ITT population for study 302, and for modified ITT populations for the other three studies.

The PBAC noted there was a statistically significant difference over placebo in responders, favouring zonisamide, in the analysis of all but one trial (912-US). There was no statistically significant difference in responders between treatments in the lamotrigine trials except Jawad (1989), which was based on very small patient numbers.

The indirect comparison showed there was a statistically significant difference in the risk difference in favour of zonisamide, but not in the risk ratio, due to the differences in placebo responder rates between zonisamide and lamotrigine.

The table below summarises various side effect parameters between zonisamide and lamotrigine using placebo as a common reference.

Event	Zon-Pbo RD (95%CI)	Zonisamide N=442 §	Placebo Zon N=350 Lam N=368	Lamotrigine N=653	Lam-Pbo RD (95%CI)	Zon-Lam RD (95%CI)
Withdrawals	0.09 (0.04, 0.15)	104 (23.5%)	46(13.1%)			0.07 (0.00, 0.14)
			36 (9.8%)	90 (13.8%)	0.02 (-0.02, 0.05)	
W'draw due to AEs	0.03 (-0.05, 0.10)	46 (10.4%)	16 (4.6%)			
Ataxia	0.04 (0.01, 0.07)	31 (7%)	8 (2.3%)			-0.07 (-0.14, 0.00)
			25 (6.8%)	143 (21.9%)	0.11 (0.04, 0.17)	
Dizziness	0.08 (0.04, 0.13)	76 (17.2%)	34 (9.7%)			-0.02 (-0.13, 0.09)
			67 (18.2%)	265 (40.6%)	0.10 (0.00, 0.19)	
Nausea	0.01 (-0.03, 0.05)	45 (10.2%)	32 (9.1%)			-0.06 (-0.12, 0.00)
			43 (11.7%)	134 (20.5%)	0.07, (0.03, 0.12)	
Fatigue	0.01 (-0.04, 0.07)	32 (7.2%)	22 (6.3%)			0.03 (-0.04, 0.10)
			41 (11.1%)	47 (7.2%)	-0.02 (-0.07, 0.02)	
Somnolence	0.10 (0.01, 0.18)	83 (18.8%)	33 (9.4%)			0.07 (-0.04, 0.18)
			34 (9.2%)	89 (13.6%)	0.03 (-0.03, 0.10)	
Agitation or irritability	0.04 (-0.02, 0.10)	39 (8.8%)	17 (4.9%)		NR	
Anorexia	0.07 (0.03, 0.11)	54 (12.2%)	16 (4.6%)		NR	
Diplopia	0.04 (0.01, 0.07)					-0.2 (-0.27, -0.13)
			18 (9.7%)	161 (33.8%)	0.24 (0.18, 0.30)	
Headache	-0.01 (-0.06, 0.04)					-0.04 (-0.13, 0.05)
			59 (31.9%)	171 (35.8%)	0.03 (-0.05, 0.11)	

In the zonisamide meta-analyses, there were significant increases in ataxia, dizziness, somnolence, anorexia and diplopia compared to placebo. In the lamotrigine meta-analyses, there were significant increases in ataxia, nausea and diplopia compared to placebo. The submission claimed that although there were some differences between zonisamide and lamotrigine across various safety parameters, these differences were small and neither drug appears clearly superior to the other from an adverse event profile perspective.

For PBAC's view of these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that zonisamide was no worse than lamotrigine.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis. The equi-effective doses in the context of cost-minimisation are zonisamide 400mg and lamotrigine 300mg. This was based on doses used in the trials in the meta-analyses.

11. Estimated PBS Usage and Financial Implications

The financial savings per year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated by the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of zonisamide for the treatment, as adjunctive therapy, of partial epileptic seizures, which are not controlled satisfactorily by other anti-epileptic drugs, on a cost-minimisation basis compared with lamotrigine.

The PBAC agreed that lamotrigine was the appropriate comparator and noted the meta-analyses of the indirect comparisons of zonisamide and lamotrigine trials which indicated zonisamide 400 mg as equi-effective as lamotrigine 300 mg.

The PBAC considered that zonisamide appears non inferior and has a no worse side effect profile compared with lamotrigine. However, the wide confidence interval of the relative risk of 1.05 (0.62, 1.76) in the indirect analysis of zonisamide and lamotrigine trials indicated there was some uncertainty in the submission's claim of zonisamide being non-inferior to lamotrigine.

The PBAC recommended the 20 day safety net rule should apply.

Recommendation

Restriction:	Authority Required (STREAMLINED) Treatment of partial epileptic seizures, which are not controlled satisfactorily by other anti-epileptic drugs.
Maximum quantity:	56 (25 mg and 50 mg) 2 x 56 (100 mg)
Repeats:	5

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

Eisai Australia welcomes the decision by the PBAC to issue a positive recommendation for Zonegran (Zonisamide, capsules, 25mg, 50mg and 100 mg,) to be made available to patients through the Pharmaceutical Benefits Scheme (PBS).