PUBLIC SUMMARY DOCUMENT
Product: Levetiracetam, tablet 250 mg, 500 mg and 1000 mg, oral solution 100 mg per mL, Keppra®
Sponsor: UCB Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application
The submission sought to extend the current PBS listing to include treatment of primary generalised tonic clonic seizures (PGTCS) and generalised myoclonic seizures [also called juvenile myoclonic epilepsy (JME)].

2. Background
At the June 2001 meeting, the PBAC recommended an authority required listing for levetiracetam tablets for treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs on a cost-minimisation basis compared with lamotrigine, with 2 g levetiracetam being similar in effectiveness and safety to 300 mg lamotrigine (drug costs only). Listing was effective from 1 August 2003.

Levetiracetam was listed as a Special Pharmaceutical Benefit from 1 August 2005, with the Special Patient Contribution applying to the restriction "Treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs" because the company did not agree to a price reduction under the 12.5% pricing policy.

At the November 2007 meeting, the PBAC recommended listing levetiracetam oral solution for the treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs in patients who have difficulty swallowing tablets.

3. Registration Status
Levetiracetam was first TGA registered on 22 February 2001 for:

- Use in epileptic patients aged 4 years and older, initially as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation.

In May 2008, the approved indications were extended to include:

- Monotherapy in the treatment of partial onset seizures, with or without secondary generalisation, in patients from 16 years of age with newly diagnosed epilepsy.
- Add-on therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy (JME).
- Add-on therapy in the treatment of PGTC seizures in adults and children from 4 years of age with idiopathic generalised epilepsy (IGE).

4. Listing Requested and PBAC's View
Authority required
Treatment of primary generalised tonic clonic seizures initially as add-on therapy and treatment of generalised myoclonic seizures initially as add-on therapy.

Alternative wording for the indication proposed by the sponsor was:

Idiopathic generalised epilepsy where the predominant seizure type is tonic clonic or myoclonic.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

In all patients with epilepsy, around 57% have partial seizures, 23% tonic clonic seizures, 6% absence seizures and 3% myoclonic seizures. The last three seizures comprise the majority of generalised seizures, with the tonic clonic variety being by far the biggest of these types, comprising around 88%.

Levetiracetam will provide an option as add-on therapy for the treatment of primary generalised tonic clonic (PGTC) seizures and myoclonic seizures

6. Comparator

The submission nominated lamotrigine and topiramate for the PGTCS indication.
The PBAC considered that the proper comparison for the PGTCS indication was with lamotrigine. No comparator was presented for the myoclonic seizures of idiopathic generalised epilepsy (IGE) indication.

7. Clinical Trials

The submission presented a single placebo-controlled randomised trial for each of levetiracetam, topiramate and lamotrigine for the primary generalised tonic clonic indication and a single placebo-controlled randomised trial of levetiracetam for the myoclonic indication.

Table B(i).2.3: Trials and associated reports presented in the submission

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Primary generalised tonic clonic seizures		
Levetiracetam versus placebo		
N01057	On behalf of Levetiracetam N01057 Study Group. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. Efficacy and safety o f levetiracetam as adjunctive treatment in adult and paediatric patients suffering from idiopathic generalised epilepsy with primary generalised tonic–clonic seizures	Berkovic SF, et al. Neurology. 2007; 69 (18): 1751-60 Morrow J. Epilepsia 2006; 47 (Suppl3) p180.
Topiramate		
Biton 1999	A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures.	Biton V, et al. Neurology 1999; 52: 1330-1337
Ben-Menachem 1997	A Double-Blind Trial of Topiramate in Patients with Generalised Tonic-Clonic Seizures of Non-Focal Origin.	Ben-Menachem E, et al. Epilepsia, 1997; 38 (Suppl 3): 60
Biton 2005	Topiramate in Patients with Juvenile Myoclonic Epilepsy,	Biton V, et al. Arch Neurol 2005; 62: 1705-1708
Lamotrigine		
Biton 2005	Double-blind, placebo-controlled study of	Biton V, et al.

	lamotrigine in primary generalized tonic-clonic seizures.	Neurology 2005; 65: 1737-1743
	Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic clonic seizures.	Trevathan E, et al. Pediatrics, 118 (2): e371-8.
Myoclonic seizures		
Levetiracetam		
Study N166	Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures.	Noachtar, et al. Neurology 2008;70: 607–616
	Efficacy and Safety of Levetiracetam 3000 mg/d as Adjunctive Treatment in Adolescents and Adults Suffering from Idiopathic Generalised Epilepsy with Myoclonic Seizures	Verdru P, et al. Eplilepsia 2005; 46 (Suppl6): 56-7
	Seizure Control with Levetiracetam in Juvenile Myoclonic Epilepsies	Andermann E, et al. Epilepsia 2005 46 (Suppl8) 205

8. Results of Trials

Key results of the randomised trials are presented below.

Primary Generalised Tonic Clonic Seizures

Median % reduction (double blind treatment period compared with baseline) rate of primary generalised tonic clonic seizures – primary outcome in all trials

	N01057		Biton 1999		Biton 2005	
	Placebo (n=84)	**LEV (n=78)**	**Placebo (n=40)**	**TOP (n=39)**	**Placebo (n=59)**	**LAM (n=58)**
Median % reduction PGTC	44.57	77.58	9.0	56.7	34.2	66.5
Median difference (95% CI) p-value	**27.99 (11.96, 39.72) <0.001**		0.019		0.06	

Abbreviations: LEV = levetiracetam; TOP = topiramate; LAM = lamotrigine

These results indicate that patients treated with levetiracetam and topiramate have a statistically significantly reduced mean reduction rate of PGTCS compared with those treated with placebo. No statistically significant differences were observed between patients treated with lamotrigine or placebo as reported in Biton (2005).

The following tables present the proportion of patients in the levetiracetam and topiramate trials, and the levetiracetam and lamotrigine trials, who achieved at least a 50 % reduction, and a 100% reduction in PGTCS rate. Indirect comparisons are also presented.

Levetiracetam vs Topiramate: Indirect Comparison of PGTC 50% and 100% Responder Rates

Trial of LEV (N01057)			**Trial of TOP (Biton 1999)**			**Indirect estimate of effect Indirect RR (95% CI)**
Treatment effect RR (95% CI)	**LEV n/N (%)**	**PBO n/N (%)**	**PBO n/N (%)**	**TOP n/N (%)**	**Treatment effect RR (95% CI)**	
PGTC 50% Responder Rate						
1.595 (1.215, 2.094)	57/79 (72.2)	38/84 (45.2)	8/*40* (*20*)	22/39 (56.4)	**2.*82* (1.*43*, 5.*56*)**	0.566 (0.272, 1.175)
PGTC 100% Responder Rate						

3.367 (1.418, 7.996)	19/79 (24.1%)	6/84 (7.1%)	2/40 (5.0%)	5/39 (12.8%)	2.56 (0.53, 12.44)	1.316 (0.204, 8.498)

Levetiracetam versus Lamotrigine: Indirect comparison of PGTC 50% and 100% responder rates

Trial of LEV (N01057)			Trial of LTG (Biton 2005)			Indirect estimate of effect Indirect RR (95% CI)
Treatment effect RR (95% CI)	LEV n/N (%)	PBO n/N (%)	PBO n/N (%)	LTG n/N (%)	Treatment effect RR (95% CI)	
PGTC 50% Responder Rate						
1.595 (1.215, 2.094)	57/79 (72.2%)	38/84 (45.2%)	23/59 (39.0%)	37/58 (63.8%)	1.636 (1.126, 2.377)	0.975 (0.614, 1.547)
PGTC 100% Responder Rate						
3.367 (1.418, 7.996)	19/79 (24.1%)	6/84 (7.1%)	10/59 (16.9%)	12/58 (20.7%)	1.221 (0.573, 2.602)	2.758 (0.874, 8.706)

All three studies demonstrated a statistically significant benefit over placebo in achieving a 50 % reduction in PGTC seizure rate. The proportion achieving PGTC seizure freedom rate (100% responders) was greater in the treatment groups compared with the placebo groups in all trials, however the difference reached statistical significance only in Trial N01057. The indirect comparisons of levetiracetam versus topiramate and lamotrigine indicate there are no statistically significant differences between the treatments in the proportion of patients achieving a 50% or 100% responder rate.

Generalised Myoclonic Seizures

50% Responder rate in myoclonic seizure days per week over the treatment period – mITT population (primary outcome)

LEV N=60 n/N (%)	PBO N=60 n/N	Odds ratio (95% CI)	(p-value)
35 (58%)	14 (23%)	**4.77 (2.12, 10.77)**	**(0.0002)**

Responders were defined as patients with at least 50% reduction of seizures. The odds of achieving a 50% response were statistically significantly greater in the treatment group than in placebo.

An indirect comparison of adverse events reported in the levetiracetam, topiramate and lamotrigine trials indicated there are no statistically significant differences between the treatments. An extended assessment revealed no other safety concerns beyond those reported in the randomised trials.

9. Clinical Claim

The submission claimed equivalency in terms of comparative effectiveness and equivalency in terms of comparative safety with topiramate and lamotrigine in primary generalised tonic clonic seizures.

The Committee considered that the proper comparison for the PGTCS indication was with lamotrigine and that the presented data generally support the claim of non-inferiority in this indication as there was no statistical difference in any of the outcomes, but the confidence intervals were wide due to small sample numbers and additionally, no non-inferiority limits had been given.

The submission did not make a therapeutic claim regarding the comparative effectiveness and safety of levetiracetam over topiramate and lamotrigine in myoclonic seizures.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The submission argued that the current therapeutic relativities of levetiracetam, topiramate and lamotrigine for partial seizures are maintained for primary generalised tonic clonic seizures (dosage data available) and although not explicitly stated, that the relativities are maintained for the myoclonic seizures (for which no dosage or comparative dosage data is provided). The table below summarises the current therapeutic relativities for the partial seizure indication and the maintenance doses reported for the primary generalised tonic clonic seizures.

Mean maintenance dose

	levetiracetam	topiramate	lamotrigine
Indirect comparison in submission	2549[a]	359	315.96
Indirect comparison – steady state only	*2887.2[b]*	*359*	*296.61*
Current therapeutic relativity	2000[c]	300mg	300mg
Ratio current trial dose to comparison trial dose	*1.44*	*1.2*	*0.99*

[a] treatment period (up-titration plus evaluation)
[b] evaluation dose, trial N01057
[c] partial seizures

The PBAC agreed with the ESC regarding the appropriate means of determining the equi-effective doses in these indications, considering that the therapeutic relativities of levetiracetam and lamotrigine for partial seizures cannot be maintained because the dose relativity of the drugs change in this indication compared to the data on partial seizures presented in earlier submissions and that because epilepsy requires chronic treatment, the dose relativity should be determined at steady state.

Listing was recommended on a cost-minimisation basis with lamotrigine with the equi-effective doses for these indications being levetiracetam 2887 mg and lamotrigine 296 mg.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS to be less than $10 million (SPC inclusive) in Year 5.

The submission estimated the likely number of patients per year to be less than 10,000 in Year 5.

12. Recommendation and Reasons

The PBAC recommended extending the authority required listing of levetiracetam on the Pharmaceutical Benefits Scheme to include the treatment of primary generalised tonic clonic seizures (PGTCS) and generalised myoclonic seizures. Listing was recommended on a cost-minimisation basis with lamotrigine with the equi-effective doses for these indications being levetiracetam 2887 mg and lamotrigine 296 mg.

In making this recommendation, the Committee considered that the proper comparison for the PGTCS indication was with lamotrigine and that the presented data generally support the claim of non-inferiority in this indication as there was no statistical difference in any of the outcomes, but the confidence intervals are wide due to small sample numbers and additionally, no non-inferiority limits have been given.

The Committee accepted that although a true cost-minimisation or cost-effectiveness analysis had not been conducted for the myoclonic seizure listing, the cross study comparison between myoclonic seizures and PGTCS indicates that the increase in the percentage of 50 % responders is similar in both cases. Furthermore the comparison between the placebo controlled trials for levetiracetam in both seizure types provided by the sponsor suggests similar improvements in the both types of epilepsy and the dose is also similar in both types. Noting that myoclonic seizures account for around 3 % of all epilepsy and taking into account the totally of the data set and the ESC advice, the Committee concluded that it is probable that the benefits of levetiracetam are similar between the two types of epilepsy and thus the data set can be used for the cost-minimisation analysis as proposed.

The PBAC however agreed with the ESC regarding the appropriate means of determining the equi-effective doses in these indications, considering that the therapeutic relativities of levetiracetam and lamotrigine for partial seizures cannot be maintained because the dose relativity of the drugs change in this indication compared to the data on partial seizures presented in earlier submissions and that because epilepsy requires chronic treatment, the dose relativity should be determined at steady state.

Finally, the Committee noted the submission's request to maintain the current Special Patient Contribution for levetiracetam for the new indications, but noted that this is a matter for policy consideration which falls outside the remit of PBAC.

Recommendation

LEVETIRACETAM, tablet, 250 mg, 500 mg, 1000 mg, oral solution 100 mg per mL

Restriction:	<u>Authority Required</u> Treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs. Treatment, as add-on therapy, of primary generalised tonic clonic seizures. Treatment, as add-on therapy, of generalised myoclonic seizures.	
Maximum quantity:	60	(tablets – all strengths)
	1	(oral solution)
Number of repeats:	5	(all 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

The sponsor disagrees with the PBAC's statement that lamotrigine is the comparator thus ignoring topiramate, especially given that there is no clinical difference at a population level between using topiramate as the comparator instead of lamotrigine. Given the disparity in view points (PBAC and sponsor) in reference to the comparator issue, the sponsor is re-evaluating its options.