

**6.05 PERAMPANEL
FILM-COATED TABLETS, 2 MG, 4 MG, 6 MG, 8 MG, 10 MG
AND 12MG
FYCOMPA®
EISAI**

1 Purpose of Application

- 1.1 The submission proposed an Authority Required (STREAMLINED) listing for perampanel for the treatment of primary generalised tonic-clonic (PGTC) seizures.

2 Requested listing

- 2.1 The Pre-Sub-Committee Response (PSCR) proposed that the requested restriction be modified from “the treatment of primary generalised tonic-clonic (PGTC) seizures” to “the treatment of Idiopathic Generalised Epilepsy with primary generalised tonic-clonic seizures.”
- 2.2 The revised proposed listing was consistent with the TGA indication in the draft Product Information (PI), which states that perampanel is indicated for treatment of PGTC seizures in patients with idiopathic generalised epilepsy (IGE).
- 2.3 In order to restrict usage to “last option add-on to the current regimen in practice”, the pre-PBAC Response proposed the following clinical criteria be included in the listing:
- The treatment must be in combination with two or more anti-epileptic drugs
 - The condition must have failed to be controlled satisfactorily by all available and reimbursed anti-epileptic drugs excluding those which are clinically contraindicated OR may exacerbate other seizure types co-existing in patients OR where adjunctive treatment is likely to significantly worsen tolerability.
- 2.4 The submission was based on a cost-effectiveness analysis of perampanel plus standard care in comparison with placebo plus standard care. Standard care refers to antiepileptic drugs (AEDs) that patients currently receive.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 Perampanel received approval by the TGA in May 2014 for the indication of:
“adjunctive treatment of partial-onset seizures with or without secondary generalised seizures in patients with epilepsy aged 12 years and older”.
- 3.2 In May 2016, the TGA indication for perampanel was extended to include:
“PGTC seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy.”

- 3.3 This was the first submission of perampanel to the PBAC for the treatment of primary generalised tonic-clonic seizures. Perampanel is listed on the PBS for the treatment of partial onset seizures.

4 Clinical place for the proposed therapy

- 4.1 PGTC seizures are clinically characterised by a sudden onset with an initial tonic phase, in which patients experience generalised muscle contraction and body stiffening, followed by a clonic phase of rhythmic clonic jerking of the face and limbs.
- 4.2 Treatment of PGTC seizures is primarily through therapy with AEDs. The management of epilepsy with multiple AEDs is a complex algorithm, with no clear lines of therapy. Following stabilisation on new adjunctive therapy, gradual withdrawal of marginally ineffective drugs from multiple anti-epileptic drug regimens may occur over time.
- 4.3 The pre-PBAC Response proposed that perampanel be used in combination with two or more anti-epileptic drugs, and that patients must have failed to be controlled satisfactorily by all available and reimbursed anti-epileptic drugs excluding those which are clinically contraindicated/may exacerbate other seizure types co-existing in patients/where adjunctive treatment is likely to significantly worsen tolerability.
- 4.4 The PBAC considered that, rather than requiring patients to have failed all available treatments, the most appropriate place in therapy for perampanel was for it to be an additional option to those currently available for the treatment of refractory patients.

5 Comparator

- 5.1 The submission nominated placebo plus standard care as the comparator for perampanel plus standard care. This would be the appropriate comparator only if perampanel was used as the last option add-on to the current regimen in practice.
- 5.2 The ESC agreed with the evaluation that perampanel will substitute for other AEDs, and noted that there are currently numerous medications listed on the PBS for primary tonic-clonic seizures, including sodium valproate, levetiracetam, lamotrigine, topiramate and oxcarbazepine. The ESC noted that the comparator for the November 2008 submission for levetiracetam for primary generalised tonic clonic seizures (and generalised myoclonic seizures) was lamotrigine.
- 5.3 The ESC recommended that further clinical advice be sought from the Epilepsy Society of Australia regarding current clinical practise. Advice was not received prior to the PBAC meeting.
- 5.4 Overall, the PBAC considered that the submission's nomination of placebo plus standard care as the comparator was not appropriate. As noted above, the PBAC considered that the most appropriate place in clinical therapy for perampanel was as an additional therapeutic option in refractory patients, and that the appropriate comparison was therefore against other therapies currently available for treating this

population. Based on information from the submission, pre-PBAC Response and clinician hearing, these therapies would include: valproate, lamotrigine, levetiracetam, and topiramate.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed how perampanel would be used in practice, and highlighted the clinical need for treatment options in this patient population. The hearing focused on the importance of having agents with different profiles available for use in the treatment of patients with epilepsy, and noted that although there are four products that are available and effective in this population, approximately 20%-40% of patients continue to suffer seizures and/or side effects. The PBAC considered that the hearing was informative as it provided a clinical perspective.

Consumer comments

6.2 The PBAC noted and welcomed the input from several organisations (3) via the Consumer Comments facility on the PBS website. The comments described the need for a variety of treatments to be available to patients with epilepsy.

Clinical trials

6.3 The submission was based on one head-to-head trial (E2007-G000-332, referred to as Trial 332 in the Commentary) comparing perampanel plus standard care to placebo plus standard care (n=164).

6.4 Details of the trial presented in the submission are provided in the table below.

Table 1: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Trial 332	A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel-Group Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures.	July 2014
	French JA et. al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial.	Neurology 2015; 85:1-8
	French JA et. al. Adjunctive perampanel for the treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients with idiopathic	Neurology 2015; 84 (14):S31.007

	generalized epilepsy (IGE): A double-blind randomized placebo-controlled phase III trial.	
	French JA et al. Adjunctive perampanel (PER) for treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients (PTS) with idiopathic generalized epilepsy (IGE): A double-blind, randomized, placebo-controlled phase III trial.	Epilepsy Currents 2015; 85:367
	Steinhoff BJ et al. Efficacy of adjunctive perampanel in idiopathic generalised epilepsy patients with drug-resistant primary generalised tonic-clonic seizures by age, sex, race: A double-blind PBO-controlled phase 3 trial.	European Journal of Neurology 2015; 22:64-65

PBO = placebo

Source: Table B.2.2, p28 of the submission

6.5 The key features of the direct randomised trial are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes ^a	Use in modelled evaluation
Perampanel plus standard care versus placebo plus standard care						
Trial 332	164 ^b	R, DB, MC 17 weeks' treatment ^c	Low	IGE patients with refractory PGTC seizures	1) Percent change from baseline in PGTC seizure frequency per 28 days during treatment; 2) Percentage of subjects experiencing a 50% or greater reduction in PGTC seizure frequency in the Maintenance Period relative to baseline (50% PGTC seizure responder rate)	The proportion of patients in each response category (seizure increase, <50% seizure reduction, 50-74% seizure reduction, 75-99% seizure reduction or seizure free) in terms of PGTC seizures was used in the model

^a For missing data, the last observation carried forward (LOCF) method was used to impute data.

^b A total of 164 patients were randomised. 2 randomised patients were subsequently excluded from the full analysis set: 1 patient in the perampanel arm did not receive treatment and 1 patient in the placebo arm did not have any post-baseline seizure data.

^c Comparative effectiveness data presented in the submission was collected during the 17-week treatment period. The CSR stated that the safety outcomes were collected up to 30 days after the last dose of treatment.

DB=double blind; MC=multi-centre; R=randomised; IGE = idiopathic generalised epilepsy; PGTC = primary generalised tonic-clonic

Source: compiled during the evaluation

6.6 The measures undertaken by investigators to minimise bias in Trial 332 appear reasonable in terms of blinding of trial participants/outcome assessors and use of a centralised randomisation procedure. However, there were some apparent differences in baseline characteristics between the perampanel and placebo treatment arms, all of which had the potential to introduce confounding:

- There was a higher proportion of patients on inducer AEDs (enzyme-inducing) in the placebo arm compared to the perampanel arm (22% vs. 11%). It is well

- established that inducer AEDs may shorten the duration of action of other co-administered AEDs, thus reducing their effectiveness^a.
- There was also more frequent use of topiramate and levetiracetam in the perampanel arm and zonisamide in the placebo arm. The impact of any potential confounding remains unclear without logistic regression analyses of responder rates adjusting for these imbalances.
- 6.7 The trial population was not representative of the population for whom the PBS listing of perampanel was sought. The proposed PBS listing required that patients had failed at least three AEDs before they were eligible for perampanel and perampanel should be initiated in combination with at least two AEDs. However, over 30% of patients in both trial arms were only on one AED at baseline. In addition, the requested listing requires patients to have failed at least three AEDs (including at least one first-line and two second adjunctive AEDs). Trial 332 only reported prior use of AEDs within 30 days before the baseline period. Therefore, whether the trial population fulfilled the PBS eligibility criterion regarding prior AED use cannot be reliably assessed.
- 6.8 The PBAC agreed with the ESC that the Trial 332 population did not match the suggested PBS population. The trial did not aim to recruit a refractory patient population with only ≥ 3 seizures required over an 8 week period on a fixed dose of at least one AED for 30 days. Overall, 33.7% of participant had received only one AED prior to entering the trial. The high proportion of '50% responders' in the placebo arm of the trial further suggests the patient population was not refractory.
- 6.9 The primary analysis was the percent change from baseline in PGTC seizure frequency per 28 days during treatment (Titration and Maintenance Periods combined), except for the purposes of European Union (EU) registration. The primary analysis for the purpose of European Union (EU) registration was the 50% responder rate ($\geq 50\%$ reduction from baseline) in PGTC seizure frequency during the Maintenance Phase. Similar analyses were conducted for myoclonic seizures, absence seizures and all types of seizures.
- 6.10 Of note, the literature strongly cautions against the use of percentage change from baseline in statistical analyses. It is statistically inefficient, fails to correct for imbalance between groups at baseline^b.
- 6.11 Since no single outcome measure captures all relevant factors, quality of life should be considered as an important patient-relevant outcome.

Comparative effectiveness

- 6.12 Table 3 below summaries the PGTC seizure frequency per 28 days and median of percent change from baseline during treatment in Trial 332.

^a Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia*. 2013;54(1):11-27.

^b Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Medical Research Methodology*. 2001;1(1):6.

Table 3: PGTC seizure frequency per 28 days and percent change from baseline during treatment – Full Analysis Set

Perampanel				Placebo				Difference ^d (95% CI)	P ^e
n/N (%)	Base-line ^a	Final ^b	% Change ^c	n/N (%)	Base-line ^a	Final ^b	% Change ^c		
Median									
81/81 (100%)	2.55	0.71	-76%	81/81 (100%)	2.50	1.57	-38%	-31% (-45%, -15%)	<0.0001
Mean (SD)									
81/81 (100%)	3.50 (2.62)	1.90 (3.30)	-57% (51%)	81/81 (100%)	3.17 (2.00)	2.87 (4.74)	-6% (185%)	NR	NR

^a The mean/median number of PGTC seizures per 28 days at pre-randomisation

^b The mean/median number of PGTC seizures per 28 days during the Titration and Maintenance Periods (combined)

^c Median or mean percentage change from baseline

For the percent change in seizure frequency per 28 days for PGTC seizures, all seizures, and primary generalised seizure subtypes, the evaluation could not verify the median or mean percentage change in each treatment arm from the summary level data presented.

^d The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method

^e The P value is based on a rank analysis of covariance with treatment and pooled country as factors, and pre-randomisation seizure frequency as a covariate.

Note: the full analysis set included all patients who were randomised, took at least one dose of study medication and had any post-baseline seizure frequency data.

CI = confidence interval; NR = not reported; PGTC = Primary Generalised Tonic-Clonic; SD = standard deviation

Source: Table B.6.1, p49 of the submission; E2007-G000-332 Table 10, p.69

- 6.13 Table 4 below summaries the results of the 50% responder rate during Maintenance Phase in Trial 332.

Table 4: 50% responder rate^a during the maintenance phase – Full Analysis Set

Perampanel, n/N (%)	Placebo, n/N (%)	RD (95% CI) Perampanel vs placebo	RR (95% CI) Perampanel vs placebo	P value Perampanel vs placebo ^b
PGTC n/N (%)				
52/81 (64.2%)	32/81 (39.5%)	24.7% (9.8%, 39.6%)	1.6 (1.2, 2.2)	0.002
Absence n/N (%)				
13/27 (48.1%)	13/33 (39.4%)	8.8% (-16.4%, 33.9%)	1.2 (0.7, 2.2)	0.47
Myoclonic n/N (%)				
10/24 (41.7%)	14/23 (60.9%)	-19.2% (-47.3%, 8.8%)	0.7 (0.4, 1.2)	0.37
All types n/N(%)				
37/81 (45.7)	28/81 (34.6)	11.1% (-3.9%, 26.1%)	1.3 (0.9, 1.9)	0.18

Italics: Derived during the evaluation

^a A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days during the Maintenance Phase from pre-randomisation

^b The P value is based on non-missing values and is from a Cochran-Mantel-Haenszel test stratified by pooled country.

CI = confidence interval; RD = risk difference; RR = relative risk

Source: Modified from Table B.6.2, p50 of the submission, Table B.6.6, p53 of the submission

- 6.14 Tables 3 and 4 above indicated that perampanel was statistically significantly superior to placebo in terms of both median percentage change in PGTC seizure frequency per 28 days from baseline and 50% PGTC seizure responder rate.

- 6.15 The European Medicines Association/Committee for Medicinal Products for Human Use (CHMP)^a in the assessment of perampanel noted that a lack of a demonstrated effect of perampanel on absence and myoclonic seizures was considered relevant given that the target population of IGE patients with PGTC seizures might well also suffer from these other seizure types. The CHMP advised that the perampanel Summary of Product Characteristics should be updated to reflect this.
- 6.16 The submission presented results of absolute and percent change in the Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P) score from baseline to Week 17. Only about 50% of randomised patients were included in this analysis and the result was underpowered to detect any statistically significant difference.

Comparative harms

- 6.17 Table 5 below summarises the incidence of adverse events for Trial 332. Table 6 presents the most frequently ($\geq 10\%$) reported treatment-emergent adverse events (TEAEs) in the perampanel group.

Table 5: Summary of key adverse events in Trial 332 – Safety Analysis Set

Category ^a	Perampanel (N=81) n (%)	Placebo (n=82) n (%)	RD (95% CI) ^b	RR (95% CI) ^b
At least one TEAE ^c	67 (82.7%)	59 (72.0%)	11% (-2%, 24%)	1.15 (0.97, 1.36)
Treatment-related TEAEs	56 (69.1%)	37 (45.1%)	24% (9%, 39%)	1.53 (1.16, 2.03)
Serious TEAEs	6 (7.4%)	7 (8.5%)	-1% (-9%, 7%)	0.87 (0.30, 2.47)
Deaths	1 (1.2%)	1 (1.2%)	0% (-3%, 3%)	1.01 (0.06, 15.91)
Other SAEs	5 (6.2%)	6 (7.3%)	-1% (-9%, 7%)	0.84 (0.27, 2.65)
TEAEs leading to study drug withdrawal	9 (11.1%)	5 (6.1%)	5% (-4%, 14%)	1.82 (0.64, 5.20)

^a For each row category, a subject with 2 or more adverse events in that category is counted only once.

^b RR and RD with 95% CI were not reported in the trial publications, but were derived by the submission from reported AE (adverse event) frequencies

^c A TEAE is defined as an adverse event that (1) emerges during treatment, having been absent at pretreatment or (2) re-emerges during treatment, having been present at pretreatment but stopped prior to treatment or (3) worsens in severity during treatment relative to the pretreatment state, when the adverse event is continuous.

CI = confidence interval; RD = risk difference; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: Table B.6.14, p62 of the submission

Table 6: Summary of treatment-emergent adverse events in Trial 332, incidence $\geq 10\%$ in the perampanel group – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Perampanel (N=81) n (%)	Placebo (n=82) n (%)	RD (95% CI) ^a	RR (95% CI) ^a
Fatigue	12 (14.8%)	5 (6.1%)	9% (-1%, 18%)	2.43 (0.90, 6.59)
Irritability	9 (11.1%)	2 (2.4%)	9% (1%, 16%)	4.56 (1.02, 20.44)
Dizziness	26 (32.1%)	5 (6.1%)	26% (15%, 37%)	5.26 (2.13, 13.03)
Somnolence	9 (11.1%)	3 (3.7%)	7% (-1%, 15%)	3.04 (0.85, 10.82)

^aEMA/518002/2015 Committee for Medicinal Products for Human Use (CHMP) Assessment report for Fycompa (perampanel).

MedDRA System Organ Class Preferred Term	Perampanel (N=81) n (%)	Placebo (n=82) n (%)	RD (95% CI) ^a	RR (95% CI) ^a
Ear and labyrinth disorders	9 (11.1%)	3 (3.7%)	7% (-1%, 15%)	3.04 (0.85, 10.82)
Psychiatric disorders ^b	20 (24.7%)	16 (19.5%)	5% (-8%, 18%)	1.27 (0.71, 2.26)

^a RR and RD with 95% CI were not reported in the trial publications, but were estimated by the submission

^b Psychiatric disorders: anxiety, depression, hallucinations, mood swings, nervousness, stress

CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; RD = risk difference; RR = relative risk

Source: Table B.6.15, pp 63, 64 of the submission

- 6.18 The number of subjects with TEAEs that resulted in discontinuation of study drug was higher in the perampanel group (n=9, 11.1%) compared with the placebo group (n=5, 6.1%).
- 6.19 The incidence of dizziness, irritability, fatigue, somnolence and psychiatric disorders was higher in the perampanel group than in the placebo group. Many of these analyses lacked adequate statistical power to detect a statistically significant difference between treatment arms. The ESC noted the higher incidence of irritability with perampanel in Trial 332, and recalled a higher incidence of aggression with perampanel when used for the treatment of partial seizures.
- 6.20 It is noted that patients at high risk of suicide were excluded from Trial 332. The US Food and Drug Administration (FDA) has stated^a that perampanel causes significant psychiatric/behavioural symptoms (including anger, aggression, and hostility) in a small number of patients, and that other AEDs (such as levetiracetam) can cause similar reactions. Therefore, longer-term safety data (beyond the duration of Trial 332) is warranted.

Benefits/harms

- 6.21 A summary of the comparative benefits and harms for perampanel plus background AEDs versus background AEDs is presented in the table below.

Table 7: Summary of comparative benefits and harms for perampanel (plus background AEDs) and PBO (plus background AEDs)

	Perampanel	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Perampanel	PBO	
Benefits						
50% PGTC seizure responder rate						
Trial 332	52/81	32/81	1.6 (1.2, 2.2)	64.2	39.5	25% (10%, 40%)
Harms						
AEs	Perampanel	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
Treatment related TEAEs	56/81	37/82	1.53 (1.16, 2.03)	69.1	45.1	24% (9%, 39%)
TEAEs leading to study drug	9/81	5/82	1.82 (0.64, 5.20)	11.1	6.1	5% (-4%, 14%)

^a FDA Centre for Drug Evaluation and Research Summary Review: Perampanel, 21 October 2012

	Perampanel	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Perampanel	PBO	
withdrawal						

* The duration of treatment is 17 weeks

** The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method

AE = adverse event; CI = confidence interval; PBO = placebo; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event

Source: Compiled during the evaluation

- 6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with perampanel in comparison to placebo;
- Approximately 25 additional patients would have $\geq 50\%$ reduction in PGTC seizure frequency from baseline over a 17-week treatment period;
 - Approximately 24 additional patients would have experienced any treatment related TEAEs over a 17-week treatment period.
 - Approximately 5 additional patients would have discontinued treatment due to TEAEs over a 17-week treatment period.

Clinical claim

- 6.23 The submission described perampanel as superior in terms of comparative effectiveness and inferior in terms of comparative safety to placebo.
- 6.24 This claim was supported by the evidence from Trial 332, in terms of 50% PGTC seizure responder rate and percentage change from baseline in PGTC seizure frequency per 28 days, for patients with idiopathic generalised epilepsy.
- 6.25 However, the population in the trial had limited applicability to the population for whom the PBS listing is sought, in terms of the number and type of prior and concomitant therapies.
- 6.26 The substantial difference in the baseline frequency of myoclonic and absence seizures made the comparison of treatment effect of perampanel on these types of seizures difficult to interpret. Therefore, the effect of perampanel on the frequency of other seizure types associated with IGE is not known.
- 6.27 Superiority of perampanel to placebo in terms of QoL was also not demonstrated by the evidence provided in the submission.
- 6.28 The long term effectiveness and safety profile of perampanel, in the treatment of PGTC seizures in patients with IGE, is unknown given that the trial duration was only 17 weeks.
- 6.29 The PBAC considered, although the claim of superior comparative effectiveness was supported in the trial population in terms of number of seizures, it was not adequately supported in the requested PBS population and it was not supported in terms of improvement in quality of life.
- 6.30 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.31 Given that placebo was not considered an appropriate comparator, the PBAC considered that the cost-utility analysis presented was not informative to the assessment of the cost-effectiveness of perampanel.
- 6.32 The submission presented a cost-utility analysis in terms of cost per additional quality-adjusted life year (QALY) gained. The model is a variation of a traditional Markov structure, including five health states – seizure free, 1-12 annual seizures, 13-52 annual seizures, 53+ annual seizures, and death (both all-cause and epilepsy-based). However, transition probabilities between these health states were not directly provided. Instead, transition probabilities were based on a mapping of categorised response categories to treatment (eg one of maintenance therapy, seizure increase, <50% reduction in seizure frequency, 50-74% reduction, 75%-99% reduction or seizure free).
- 6.33 Patients enter the model into two health states corresponding to the baseline seizure frequency defined post-hoc from Trial 332 (53+ annual seizures and 12-52 annual seizures). For the first cycle, the proportion of patients in each treatment response category was derived from Trial 332 and used to estimate the transition probabilities. While from the second cycle onward until the end of the model, transition probabilities were estimated from Neligan et al 2012 (except the transition probability from ‘<50%’ to ‘increase in seizures’ which was based on Trial 332, as this category was not included in Neligan et al 2012).
- 6.34 From cycle 2 onward, if patients experience an increase in seizure frequency, in the next cycle:
- Patients in the perampanel arm will be assumed to withdraw from perampanel and enter the maintenance therapy category and stay in that category until the end of the model while assuming no further change in seizure frequency; and
 - Patients in the placebo arm, if experiencing an increase in seizure frequency, have their treatment assumed to be unchanged but they move to and remain in the maintenance category without further change in seizure frequency.
- 6.35 Patients were assumed to have an increased risk of death with an increase in seizure frequency, based on Nilsson et al 1999 and to also experience all-cause mortality.
- 6.36 Without providing any justification, the submission further assumed an average response rate for each category of response (eg. <50% reduction was assumed to have an average of 25% reduction in seizures, an average of 62.5% reduction in 50-74% category, and 87.5% in 75-99% reduction category, implying a symmetrical distribution in each category, which would suggest an unusual shape to the distribution of seizure frequency reduction overall).

Table 8: Summary of model structure and rationale

Time horizon	50 years in the model, compared to 17 weeks in the trial
Outcomes	QALYs, LYG and seizures avoided
Methods used to generate results	Cohort expected value analysis
Cycle length	4 months

Transition probabilities	The transition probabilities between categories of treatment response (initiation of treatment, maintenance therapy, seizure increase, <50% reduction in seizure frequency, 50-74% reduction, 75%-99% reduction or seizure free) were estimated. For the first cycle, the proportion of patients in each treatment response category was estimated from Trial 332, while from second cycle onward until the end of the model, transition probabilities were estimated from Neligan et al 2012 (except the transition probability from '<50%' to 'increase in seizures' that were based on Trial 332, in the absence of such data in Neligan et al 2012). Relative risk of mortality based on number of seizures per year was also based on the literature (Nilsson et al 1999).
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: Compiled during the evaluation

- 6.37 A summary of the alive health state mappings based on baseline seizure frequency and response category is provided in Table 9 below.

Table 9: Health state mappings of baseline seizure frequency and response category used in the base case

From health state	To health state mapping			To health state
	% change category	Assumed avg. reduction*	# seizures after response	
53 + seizures (220.7 seizures annually)	Maintenance therapy	NA	NA	53+ annual seizures
	Seizures increase	Perampanel: 43.8% Background AEDs: 51.6%	Perampanel: 317 Background AEDs: 335	
	<50% response	25%	165.5	
	50-74% response	62.5%	82.8	
	75-99% response	87.5%	27.6	
	seizure free	100%	0	13-52 annual seizures
13-52 annual seizures (31.3 annual seizures)	Maintenance therapy	NA	NA	13-52 annual seizures
	seizures increase	Perampanel: 43.8% Background AEDs: 51.6%NA	Perampanel: 45 Background AEDs: 47	
	<50% response	-25%	23.5	
	50-74% response	-62.5%	11.7	1-12 annual seizures
	75-99% response	-87.5%	3.9	
	seizure free	-100%	0	seizure free

NA = not applicable

*no justification was provided in the submission for using these mid-point estimates

Source: compiled during the evaluation

- 6.38 The population in the model may not have been representative of the population for whom the PBS listing was sought, in terms of the number and type of prior and concomitant AEDs.
- 6.39 The submission assumed that the proposed PBS population was likely to be older than the PGTC trial populations and an average age of 45 years old was applied in the model, consistent with the US surveyed population in Gupta et al (2016). It was uncertain whether the refractory population requested in the proposed PBS listing for perampanel would be younger or older than a general population with PGTC seizures in the context of IGE, particularly given the increased mortality in patients

experiencing an increased number of seizures per annum. The model was moderately sensitive to this variable, given the application of an increased relative risk of dying for those who are not seizure free.

- 6.40 The model structure, application and extrapolation of treatment effect was inappropriate and did not reflect the cost-effectiveness of perampanel in patients experiencing PGTC seizures who are diagnosed with IGE:
- 6.41 There were a number of concerns regarding the structure of the model:
- The definition of health states in terms of the frequency of all seizure types used arbitrary thresholds and wide ranges; as did the definition of response categories.
 - This definition might not have captured important differences in quality of life, mortality and resource use between different types of seizures (eg absence vs myoclonic vs PGTC).
 - The assumed average reduction in seizure frequency was not justified by the submission and implied some strong assumptions regarding the frequency distribution, which were not supported by data from Trial 332; and
 - The structure of the economic model suggested that once patients experience an increase in seizures, their seizure frequency would be unchanged until the end of the model or until they die, but with reducing cost of AEDs in the perampanel arm and unchanged cost in the placebo arm. Again, this assumption was not justified. The assumption that patients do not experience disease improvement after they enter the 'increase in seizures' response category did not reflect clinical practice where patients may reduce their seizure burden upon trialling further treatment options (pharmaceutical and/or surgical) after an episode of treatment failure.
- 6.42 There were concerns over the treatment effect of perampanel applied in the model:
- The submission applied the response rate for PGTC seizure types only, not for all seizure types, to the health states. The frequency of PGTC seizures relative to all seizure types was small (eg mean of 3.2 PGTC seizures vs 33.6 all types seizures in the placebo arm, or 3.5 vs 64.4 seizures in the perampanel arm). See Section D.4; and
 - The submission assumed that the same response rates apply, irrespective of baseline seizure frequency.
- 6.43 There were concerns regarding the extrapolation of short-term treatment effect:
- Probabilities of remaining in the response states beyond 4 months are based on the proportions of a small number of patients in those response states at 18 months who remained in those states after a mean follow-up of 6.7 years [Neligan, 2012]: being in a response state at 18 months is different to being in a response state at 4 months.
 - The model uses the least relevant and most optimistic data to estimate long-term transition probabilities (e.g. 64% remain seizure free at five years). The Kaplan Meier analysis showed that “the probability of remaining seizure free at five years after entering seizure freedom was 0.48”, whilst it is also reported that “of the 45 people who achieved at least 1 year seizure freedom, ... 56% subsequently relapsed
 - Patients did not stay in the response states after a single new drug introduction, they continued starting new drugs over the intervening period.

- Constant transition probabilities were assumed over the entirety of the time horizon. This was not justified by the submission;
- The transition probability between the '<50% reduction' and 'increase in seizures' response categories was taken from the 17 week trial (Trial 332). The submission assumed that the same proportion of people who would have otherwise remained in the <50% reduction response category would experience an increase in seizure frequency for each subsequent cycle (eg a constant failure rate for each subsequent cycle over the time horizon of the model). Given that this proportion differed by treatment arm, this resulted in an amplified absolute difference in the number of treatment failures between the two arms over the time horizon of the model. The ESC noted applying the placebo probabilities to the perampanel arm reduced the ICER from \$49k to \$46k which is a counterintuitive result and suggests the model may not be internally valid.

- 6.44 Relative risk of mortality applied to patients who are not seizure free was taken from a retrospective case-control study conducted approximately 25-35 years ago in a population with a diagnosis of epilepsy (not restricted to primary generalised seizures or idiopathic epilepsy) (Nilsson et al 1999). The cases and controls in this study were not matched for potential prognostic factors, which may have led to potential confounding and bias. Furthermore, the treatment algorithm and available AED treatments have greatly changed since the study period (1980-1991) which may impact on the results.
- 6.45 Health state utilities were based on a single-page publication (de Kinderen 2014), which used a vignette-based time trade-off study to derive utility weights from a general population sample. The vignettes distinguished between frequency of seizures (seizure free, once a month, once a week, twice a week, once a day and twice a day) and seizure severity. The reported values appear to have face validity, but their application via percentage reductions in seizures reduces transparency.
- 6.46 The key drivers of the model are summarised below in Table 10

Table 10: Key drivers of the model

Description	Method/Value	Impact
Model structure	States represent mix of seizure types, wide and arbitrary ranges, and requires manipulation of percentage reductions in seizure frequencies to apply treatment effects	Unknown
Transition probabilities beyond 4 months	Data source of limited relevance and analyses of those data favourable to perampanel	High, ongoing use of the rate favours perampanel
Relative risk of mortality	1-12 annual seizures: 7.21 13-52 annual seizures: 8.64 53+ annual seizures: 10.16	Moderate, increasing mortality risk associated with seizures favours perampanel

Source: compiled during the evaluation

- 6.47 The results of the economic model are summarised in the table below. The ESC noted the QALY gains are driven by the LY gains.

Table 11: Results of the economic evaluation

	perampanel +AEDs	AEDs	Incremental
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Number of seizures	[REDACTED]	[REDACTED]	[REDACTED]

LYG	12.22	11.85	0.37
QALY	8.46	8.02	0.44
ICER per Seizure Avoided		\$█	
ICER per LYG		\$█	
ICER per QALY gained		\$█	

AED = antiepileptic drug; LYG = life year gained; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Source: Table D.5.4, p125 Section D of the submission

The redacted table shows an ICER in the range of \$45,000/QALY - \$75,000/QALY.

- 6.48 A trial-based evaluation was conducted during the evaluation, using only the direct pharmaceutical costs. Costs associated with background AEDs have been excluded from this analysis under the assumption that background AED use will be the same in the two arms. This assumption is uncertain, particularly given that the proposed listing allows perampanel monotherapy in the continuation phase of treatment. However, the cost of background AEDs is likely to be small in comparison with the cost of perampanel. In addition, concerns remain regarding the applicability of the trial population to the proposed PBS population, which may impact the results. Results of the trial-based analysis are summarised below.

Table 12: Trial-based cost per additional responder (PGTC seizures) and cost per additional PGTC seizure-free person over 17 weeks.

Component	Perampanel	Placebo	Increment
Incremental cost/extra responder (PGTC seizures) over 17 weeks			
Costs	\$█	\$█	\$█
50% response rate (PGTC seizures) ^a	52/81 (64.2)	32/81 (39.5)	0.25
Incremental cost/extra PGTC seizure-free person over 17 weeks			
Costs	\$█	\$█	\$█
PGTC seizure-free status ^b	25/81 (30.9)	10/81 (12.3)	0.19
Incremental cost/extra PGTC seizure free person over 17 weeks			
			\$█

^aTable 14.2.1.7, p447, Trial 332 CSR

^bTable 14.2.1.14, p501 of Trial 332 CSR

PGTC = primary generalised tonic clonic

Source: compiled during the evaluation

The redacted table shows an incremental cost/extra PGTC seizure free person over 17 weeks is less than \$15,000.

- 6.49 During the evaluation, a number of sensitivity analyses were conducted and it was found that the model was very sensitive to the transition probability from ‘<50% response’ to ‘increase in seizures’ response categories. The assumption that a constant proportion of patients would continue to fail treatment (i.e. experience an increase in seizures from previously achieving a <50% response) in each subsequent cycle, coupled with the assumption that patients who experience an increase in seizures will be assumed to move to ‘maintenance therapy’ category where their seizure frequency will be unchanged until death, benefited the perampanel arm. As soon as patients experienced an increase in seizures, patients in the perampanel arm were assumed to continue experiencing the same baseline number of seizures (i.e. no change to utility or non-pharmaceutical health state costs) and are expected to discontinue treatment with perampanel (reducing the average cost per cycle by \$█, from \$█). By year 6 (cycle 18), approximately 40% of the patients in the perampanel arm had failed treatment and had discontinued

perampanel. Although not explicitly stated in Neligan et al, it was likely that the ‘<50% reduction’ category also included those who had experienced an increase in seizures compared to baseline. Removing the transition probability from the ‘<50% reduction’ to ‘seizure increase’ response categories subsequent to the first cycle increases the ICER to \$75,000/QALY - \$105,000/QALY.

- 6.50 Given the fundamental uncertainty of the economic model in terms of model structure and of key inputs (including transition probabilities, risk of death and utility values), the results of the model and any sensitivity analysis should be interpreted with caution.

Drug cost/patient/day: \$ [REDACTED]

- 6.51 \$ [REDACTED] / day, for a dose of [REDACTED] mg / day (based on a DPMQ of \$ [REDACTED] for a pack of 28 tablets). Patients responding to perampanel would be expected to continue taking perampanel indefinitely due to the chronic nature of the disease.

Estimated PBS usage & financial implications

- 6.52 This submission was not considered by DUSC.
- 6.53 The submission used an epidemiological approach to estimate the financial impact of extending the current PBS listing of perampanel to include patients aged 12 years and older with epilepsy and PGTC seizures who have failed treatment with at least three AEDs (two of which must be second-line adjunctive agents).

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market Share – prevalent cases	20%	25%	30%	35%	45%
Market share – incident cases	20%	30%	40%	50%	60%
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS and other government budgets					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to other government budgets	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Assuming distribution of perampanel strengths as estimated in the submission.

Source: Fycompa PGTC_Section E FINAL.xlsx

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 - \$20 million per year.

- 6.54 The number of patients eligible for treatment with perampanel may not be as predicted in the submission. The prevalence rate of epilepsy applied in the submission is likely to be underestimated. Meanwhile, the proportion of epilepsy patients failing previous AEDs is likely to be overestimated.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of perampanel for treatment of primary generalised tonic-clonic (PGTC) seizures, on the basis of a lack of clinical data in the requested PBS population and unknown cost-effectiveness. In making this recommendation, the PBAC acknowledged the clinical need for additional therapeutic options for patients whose symptoms are not well controlled with the treatments currently available. The PBAC considered that the submission's analysis of perampanel as a last-line therapy (ie against placebo) was not an appropriate reflection of its likely place in therapy (as an additional option for refractory patients) and noted that the evidence provided in the submission did not address the refractory population
- 7.2 The PBAC considered that the submission's proposal to restrict PBS subsidy of perampanel to use as a last option add-on to the patients' current regimen, and the requirement in the proposed listing for patients' condition to have failed to have been controlled satisfactorily by all available and reimbursed anti-epileptic drugs, was not well justified. Instead, the Committee considered that the appropriate place in therapy was as an additional option to those currently available for the treatment of refractory patients.
- 7.3 Given their view on the appropriate clinical place for perampanel, the PBAC considered that the submission's nomination of placebo as the comparator was not appropriate. The Committee considered that a comparison with other treatments currently available for treatment refractory patients would be more appropriate. These treatments would include valproate, lamotrigine, levetiracetam, and topiramate.
- 7.4 The PBAC noted that the clinical trials provided in the submission did not match the requested PBS population. In particular, the Committee noted that trial data indicated that over 30% of patients in both trial arms were only on one AED at baseline. In addition, the requested listing requires patients to have failed at least three AEDs (including at least one first-line and two second adjunctive AEDs). Trial 332 only reported prior use of AEDs within 30 days before the baseline period. Therefore, whether the trial population fulfilled the PBS eligibility criterion regarding prior AED use cannot be reliably assessed. Therefore, the PBAC considered that the applicability of the population in Trial 332 to the proposed PBS population remains uncertain.
- 7.5 The PBAC considered, although the claim of superior comparative effectiveness was supported in the trial population in terms of number of seizures, it was not adequately supported in the requested PBS population and it was not supported in terms of improvement in quality of life.
- 7.6 The PBAC considered that the claim of inferior comparative safety was reasonable.
- 7.7 Given that placebo was not considered an appropriate comparator, the PBAC considered that the cost-utility analysis presented was not informative to the

assessment of the cost-effectiveness of perampanel. The Committee considered that a comparison against other active treatments used for refractory patients would be more appropriate.

- 7.8 Notwithstanding the issues with the appropriateness of the presentation of a cost-utility analysis against placebo, the PBAC noted a number of issues raised with the economic analysis presented, as detailed in Section 6 of this public summary document. These included issues with:
- The structure of the model
 - The treatment effect of perampanel applied in the model
 - The extrapolation of the treatment effect observed in the study
 - The mortality risk applied in the model
 - The validity of the health state utilities applied in the model

- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.