# 7.06 PERAMPANEL, Film-coated tablets, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg, Fycompa®, Eisai Australia Pty Ltd

## 1 Purpose of application

1.1 The re-submission proposed an Authority Required (STREAMLINED) listing for perampanel for the treatment of Idiopathic Generalised Epilepsy (IGE) with primary generalised tonic-clonic (PGTC) seizures. The first submission was considered by the PBAC in July 2016.

**Table 1: Key components of the clinical issues addressed by the re-submission**

| Component | Description |
|---|---|
| Population | Idiopathic Generalised Epilepsy (IGE) patients with Primary Generalised Tonic-Clonic (PGTC) seizures |
| Intervention | Perampanel tablets taken orally once daily before bedtime. Initial dose of 2mg/day, increased to a maintenance dose of up to 8mg/day. The dose may be increased up to a maximum of 12mg/day depending upon clinical response and tolerability. |
| Comparator | Mixed comparators – (i) placebo for use as a last option add-on treatment and (ii) other antiepileptic drugs (AEDs) (individually) when used as an additional option to the currently used AEDs |
| Outcomes | The percent change from baseline in PGTC or GTC seizure frequency, the 50% PGTC or GTC seizure responder rate, defined as the percentage of subjects experiencing a 50% or greater reduction in PGTC or GTC seizure frequency relative to baseline, and treatment-emergent adverse events (TEAEs). |
| Clinical claim | Perampanel versus placebo: perampanel (plus standard care, i.e. background AEDs) is superior to placebo (plus standard care) in terms of efficacy and inferior to placebo (plus standard care) in terms of safety.<br>Perampanel versus lamotrigine or levetiracetam: perampanel (plus standard care) is non-inferior, in terms of both comparative effectiveness and comparative safety, to either lamotrigine (plus standard care) or levetiracetam (plus standard care). |

Source: Compiled during the evaluation

## 2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer | |
|---|---|---|---|---|---|
| PERAMPENAL<br>2 mg tablet, 7 | 2 | 1 | $[redacted] | Fycompa® | Eisai Australia Pty Ltd |

| | |
|---|---|
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives |
| **Severity:** | *Primary generalised tonic-clonic seizures* |
| **Condition:** | Idiopathic generalised epilepsy ~~with Primary Generalised Tonic-Clonic seizures~~ |
| **PBS Indication:** | *Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures* |
| **Treatment phase:** | Initial ~~therapy~~ |
| **Restriction Level / Method:** | ☐ Restricted benefit<br>☐ Authority Required - In Writing<br>☐ Authority Required - Telephone<br>☐ Authority Required - Emergency<br>☐ Authority Required - Electronic<br>☒ Streamlined |
| **Treatment criteria:** | Must be treated by a neurologist |
| **Clinical criteria:** | The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs,<br><br>AND<br><br>*The treatment m*~~M~~ust be in combination with at least one *PBS subsidised* anti-epileptic drug,<br><br>AND<br><br>The treatment must be for dose titration purposes ~~(2mg, 7 packs sizes only)~~. |
| **Population criteria:** | Patient must be aged 12 years or older. |
| **Administrative Advice** | No ~~applications for~~ increase~~d~~ *to the* maximum quantities will be authorised. |

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer | |
|---|---|---|---|---|---|
| PERAMPENAL | | | | | |
| 4 mg tablet, 28 | 1 | 2 | $[redacted] | Fycompa® | Eisai Australia Pty Ltd |
| 6 mg tablet, 28 | 1 | 2 | $[redacted] | | |
| 8 mg tablet, 28 | 1 | 5 | $[redacted] | | |
| 10 mg tablet, 28 | 1 | 5 | $[redacted] | | |
| 12 mg tablet, 28 | 1 | 5 | $[redacted] | | |

| | |
|---|---|
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | ☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives |
| **Severity:** | *Primary generalised tonic-clonic seizures* |
| **Condition:** | Idiopathic Generalised epilepsy ~~with Primary Generalised Tonic-Clonic seizures~~ |
| **PBS Indication:**<br><br>*PBS Indication is the combination of the Episodicity, Severity and Condition.* | *Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures* |
| **Treatment phase:** | Continuing ~~therapy~~ |
| **Restriction Level / Method:** | ☐ Restricted benefit<br>☐ Authority Required - In Writing<br>☐ Authority Required - Telephone<br>☐ Authority Required - Emergency<br>☐ Authority Required - Electronic<br>☒ Streamlined |
| **Treatment criteria:** | ~~For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.~~ |
| **Clinical criteria:** | Patient must have previously been ~~treated with PBS subsidised perampanel.~~<br>*issued with an authority prescription for this drug* |
| **Population criteria:** | Patient must be aged 12 years or older. |
| **Administrative Advice** | No ~~applications for~~ increase~~d~~ *to the* maximum quantities will be authorised.<br>*For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.* |

2.1 The re-submission was based on:

- A cost-minimisation analysis of perampanel plus standard care compared with other anti-epileptic drugs (AEDs) (represented by lamotrigine or levetiracetam) plus standard care; and
- A cost-utility analysis of perampanel plus standard care compared with placebo plus standard care. Standard care refers to AEDs that patients currently receive.

2.2 The recommended dose regimen for perampanel for the treatment of PGTC seizures in patients ≥ 12 years old with IGE is an initial dose of 2mg/day, which may be

increased based on clinical response and tolerability, by increments of 2mg/day, weekly or fortnightly, to a maintenance dose of up to 8mg/day. Depending upon clinical response and tolerability at a dose of 8mg/day, the dose may be increased up to a maximum of 12mg/day. Perampanel tablets are to be taken once daily before bedtime.

2.3 The re-submission proposed a special pricing arrangement with a confidential price for perampanel for this indication. Based on the weighted pricing analysis across 'substituted use' and 'last line use' of perampanel, the Sponsor proposed a confidential dispensed price of $[redacted] for the 8mg, 10mg, and 12mg packs (i.e. flat pricing as per the current PBS listing). No special pricing arrangement was proposed for the 2mg, 4mg and 6mg packs, which are sub-therapeutic doses intended only for titration in the PGTC seizure indication.

2.4 Compared to the original submission, the listing for the initial treatment phase proposed in the re-submission has been revised to reduce the number of AEDs that a patient is required to have failed before being eligible for perampanel from at least three to at least two, and reduce the minimum number of AEDs that perampanel must be used in combination with from two to one.

2.5 The PSCR to the original submission proposed that patients must have failed to be controlled satisfactorily by all available and reimbursed AEDs unless those AEDs are contraindicated, could exacerbate other seizure types, or could worsen tolerability. The revised restriction allows perampanel to be used as an earlier line of treatment. The PBAC noted that this is consistent with its earlier consideration that "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" (Paragraph 4.4, Item 6.05, Perampanel PSD, July 2016).

2.6 The ESC noted the requirement in the proposed restriction that the condition must have failed to be controlled satisfactorily by at least two AEDs was not well justified given 33.7% of Trial 332 participants were treated with only one AED at baseline.

2.7 The pre-PBAC Response stated that trial 332 included a heavily pre-treated and refractory population, with 20% of patients taking three or more AEDs and 46% of patients taking two AEDs at study baseline. It argued that while the number of AEDs ever tried by patients was not collected, given the median length of time since diagnosis (14 years) and the inclusion criteria for the trial (a minimum of 3 seizures in the 8 week period prior), it was not unreasonable to infer that most, if not all, suitable treatments had previously been tried by patients.

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

# 3 Background

3.1 TGA status: 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 second submission of perampanel to the PBAC for the treatment of PGTC seizures in patients with IGE. Perampanel is listed on the PBS for the treatment of partial onset seizures.

3.4 The major outstanding matters of concern from the previous submission are summarised in Table 2 below.

**Table 2: Summary of outstanding matters of concern**

| Matters of concern | How the resubmission addressed it |
|---|---|
| The submission's analysis of perampanel as a last-line therapy (i.e. against placebo) was not an appropriate reflection of its likely place in therapy (as an additional option for refractory patients). The Committee considered that a comparison with other treatments currently available for treatment of refractory patients would be more appropriate. These treatments would include valproate, lamotrigine, levetiracetam, and topiramate (Paragraphs 7.1 and 7.3, Item 6.05, Perampanel PSD, July 2016). | The re-submission proposed two distinct clinical places of therapy<br>(1) Perampanel (plus standard care) as a last option add-on to the current regimen for patients who are refractory to or have exhausted all currently available treatments (e.g. last-line use – the same as the July 2016 submission). Supported by a cost-utility analysis, and<br>(2) Perampanel (plus standard care) as an additional option to those currently available for the treatment of refractory patients. This was supported by indirect comparisons of perampanel with lamotrigine or levetiracetam, and a cost-minimisation analysis of perampanel versus levetiracetam, lamotrigine, topiramate and valproate.<br>The results of these analyses were then used to calculate a weighted ex-manufacturer price of 8mg of perampanel. The proportion of expected use of perampanel as a substituted drug (perampanel vs. other AEDs), and as a last-line therapy (perampanel vs. placebo) were obtained from a survey of epileptologists conducted by the re-submission, and used to weight the proposed price of perampanel. |
| The PBAC reflected that the clinical trials provided in the major submission did not match the requested PBS population and that patients in these trials were unlikely to be 'refractory'. (Paragraph 7.1 & 7.4, Item 6.05 perampanel PSD, July 2016 Meeting). | The listing for the initial treatment phase has been revised to:<br>• Reduce the number of AEDs that a patient is required to have failed before being eligible for perampanel from at least three to at least two; and<br>• Reduce the minimum number of AEDs that perampanel must be used in combination with from two to one.<br>However, the re-submission maintained its request for last line treatment of perampanel, using the same Trial 332 as the key clinical evidence in comparison with placebo, in addition to requesting perampanel as an earlier line of therapy, again |

| Matters of concern | How the resubmission addressed it |
|---|---|
| | using the same evidence of Trial 332 in the indirect comparison with other AEDs. |
| 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. (Paragraph 7.5, Item 6.05, perampanel PSD, July 2016). | This issue remains for the comparison of perampanel with placebo. |
| 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. These included issues with:<br>• The structure of the model<br>• The treatment effect of perampanel applied in the model<br>• The extrapolation of the treatment effect observed in the study<br>• The mortality risk applied in the model<br>• The validity of the health state utilities applied in the model<br>(Paragraph 7.8, Item 6.05 perampanel PSD, July 2016 Meeting). | Although the re-submission updated a few input variables and corrected the error identified with the previous submission, the key concerns relating to the economic model remain outstanding and have not been addressed in the re-submission. |

AED = anti-epileptic drug; QoL = quality of life; PGTC = primary generalised tonic-clonic

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

# 4 Population and disease

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 clearly demarcated lines of therapy. Following stabilisation on new adjunctive therapy, gradual withdrawal of marginally ineffective drugs from multiple AED regimens may occur over time.

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

# 5 Comparator

5.1 Although the re-submission revised its requested restriction to allow perampanel to be used as an early line of therapy, the re-submission proposed two distinct clinical places of therapy, and hence two different comparators, for perampanel:

(1) Perampanel (plus standard care, i.e. including background AEDs) as a last option add-on to the current regimen for patients who are refractory to or have exhausted all currently available treatments, where the nominated comparator is placebo (plus standard care), and

(2) Perampanel (plus standard care) as an additional option to those currently available for the treatment of refractory patients, where the nominated comparator is another adjunctive AED treatment, represented by either lamotrigine (plus standard care) or levetiracetam (plus standard care), that may be substituted by perampanel.

5.2 The ESC noted that in its previous consideration of perampanel (July 2016) the PBAC stated that the submission's nomination of placebo plus standard care as the comparator was not appropriate. At that time, 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, including valproate, lamotrigine, levetiracetam, and topiramate (paragraph 5.4, Item 6.05, perampanel PSD, July 2016).

5.3 The ESC considered that the choice of comparators for the cost-minimisation analysis was not well justified; however, it noted the July 2016 PBAC advice that valproate, lamotrigine, levetiracetam and topiramate may be relevant comparators.

5.4 The ESC recommended the PBAC should consider whether a cost-minimisation against a mixed basket of comparators with different PBS prices is a relevant approach.

5.5 The Pre-Sub-Committee Response (PSCR) stated the sponsor is willing to work with the Department to reach an agreement on an appropriate split between the comparators of placebo and other PBS listed AEDs

5.6 Overall, the PBAC maintained the view that a comparison wholly against placebo was not appropriate. However, on balance – noting the clinical need for another therapeutic option in refractory patients – it considered that the approach of a mixed comparison against placebo for patients who have failed to respond adequately to existing treatment options and against other currently available AEDs (valproate, lamotrigine, levetiracetam and topiramate) for patients in whom perampanel will substitute for another AED could be acceptable - subject to changes to the proportion of patients in each comparator group presented in the submission.

*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 presenter discussed the clinical need for an additional treatment option for patients with PGTC seizures and how the drug would be used in practice – noting that they believed use would be predominantly last line. The presenter acknowledged that there is uncertainty in the model; however, they also stated that it is challenging to model epilepsy and that any model, based on currently available data, will contain a level of uncertainty. They further noted that any future resubmissions to address the model would be unlikely to provide substantially different outcomes. In addition to the hearing the sponsor provided a written expert clinician opinion statement to members. The statement noted that currently appropriate treatment options for patients with PGTC seizures in IGE can be quite limited. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

## *Consumer comments*

6.2 The PBAC noted that no consumer comments were received for this item.

## *Clinical trials*

6.3 The re-submission was based on one head-to-head trial (E2007-G000-332, referred to as Trial 332) comparing perampanel plus standard care to placebo plus standard care (n=164). This trial is the same as that presented in the previous submission and was considered by the PBAC in July 2016.

6.4 The re-submission was also based on indirect comparisons of perampanel versus lamotrigine or levetiracetam via one perampanel trial (Trial 332), two lamotrigine trials (Biton 2005 and Biton 2010 trials) and one levetiracetam trial (Berkovic 2007 trial) with placebo as the common reference.

- Biton 2005, a randomized placebo controlled trial evaluating the efficacy and safety of adjunctive lamotrigine immediate-release (IR) in epileptic patients with PGTC seizures (dose of lamotrigine depended on patient age and concomitant AEDs) (n=121); it was not clear whether patients had to have IGE to be included in this trial.
- Biton 2010, a randomized placebo controlled trial evaluating the efficacy and safety of adjunctive lamotrigine extended-release (XR) in epileptic patients with PGTC seizures; extended-release lamotrigine is not listed on the TGA Australian Register of Therapeutic Goods (ARTG) and, therefore, Biton 2010 has been excluded from evaluation.

- Berkovic 2007, a randomized placebo controlled trial evaluating the efficacy and safety of adjunctive levetiracetam in patients with generalised tonic-clonic (GTC) seizures associated with IGE (n=164).

6.5 Details of the trials presented in the re-submission are provided in the table below.

**Table 3: Trials and associated reports presented in the re-submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Direct trial, and used in the indirect comparisons** | | |
| **Perampanel versus placebo** | | |
| Trial 332 | Clinical study report.<br>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.<br>French JA et. al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial.<br>French JA et. al. Adjunctive perampanel for the treatment of drug-resistant primary generalized tonic-clonic (PGTC) seizures in patients with idiopathic generalized epilepsy (IGE): A double-blind randomized placebo-controlled phase III trial.<br>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.<br>French et al. Adjunctive perampanel RCT for PGTC seizures.<br>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.<br>Krauss et al. Relationship between perampanel exposure, seizure outcomes and treatment-emergent adverse events (TEAEs) in patients with primary generalized tonic-clonic seizures (PGTCS): A randomised, double-blind (DB) phase III study. | 18 July 2014<br>Neurology 2015; 85:1-8<br>Neurology 2015; 84 (14):S31.007<br>Epilepsy Currents 2015; 85:367<br>Journal of Neurology, Neurosurgery and Psychiatry 2015; 86 (11)<br>European Journal of Neurology 2015; 22:64-65<br>Neurology 2016; 86(16) |
| **Indirect comparisons** | | |
| **Lamotrigine versus placebo** | | |
| Biton 2005 | Biton, et al. Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures. | Neurology 2005; 65(11): 1737-1743 |
| Biton 2010[a] | Biton et al. Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomised, placebo-controlled study. | Epilepsy Behav 2010; 19(3): 352-358. |
| **Levetiracetam versus placebo** | | |
| Berkovic 2007 | Berkovic et al. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. | Neurology 2005; 65(11): 1737-1743 |

[a] Biton 2010 is not evaluated in the Commentary (Section B(i).2) because extended-release lamotrigine is not listed on the TGA Australian Register of Therapeutic Goods (ARTG).
Source: Table B.4.2, pp49-50, of the re-submission

6.6 The key features of the randomised trials (for the direct comparison with placebo and the indirect comparisons with lamotrigine or levetiracetam) are summarised in the table below.

**Table 4: Key features of the included evidence – direct and indirect comparisons**

| Trial | N | Design/ duration of follow-up | Risk of bias | Patient population | Outcomes | Use in modelled evaluation |
|---|---|---|---|---|---|---|
| Perampanel plus standard care vs. placebo plus standard care | | | | | | |
| Trial 332[a] | 164[b] | R, DB, MC Treatment: 17 weeks[c]; Follow-up: 4 weeks[d] | 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 per 28 days 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 |
| Lamotrigine plus standard care vs. placebo plus standard care | | | | | | |
| Biton 2005 | 121[e] | R, DB, MC Treatment: 24 weeks (2–12 years) 19 weeks (≥12 years); Follow-up: 2 weeks[d] | Low/unclear[h] | Epilepsy patients[f] with PGTC seizures | Percent change from baseline in PGTC seizure frequency per month (escalation and maintenance phases separately and for the phases combined) | NA |
| Levetiracetam plus standard care vs placebo plus standard care | | | | | | |
| Berkovic 2007 | 165[g] | R, DB, MC Treatment: 24 weeks; Follow-up: 6 weeks[d] | Low/unclear[h] | IGE patients with GTC seizures | Percent change from baseline in GTC seizure frequency per week over the 24 week treatment period | NA |

[a] For missing data, the last observation carried forward (LOCF) method was used to impute data.
[b] A total of 164 patients were randomised. Two randomised patients were subsequently excluded from the Full Analysis Set: one patient in the perampanel arm did not receive treatment and one 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.
[d] Duration of follow-up for subjects not entering into an optional extension study.
[e] Four patients were randomised but not treated.
[f] It was not clear whether all patients had IGE in the Biton 2005 trial;
[g] One patient in the levetiracetam arm was randomised but not treated.
[h] Unclear risk of bias: Biton 2005 and Berkovic 2007: insufficient information to permit judgement
DB=double blind; MC=multi-centre; R=randomised; IGE = idiopathic generalised epilepsy; PGTC = primary generalised tonic-clonic; GTC = generalised tonic clonic, NA = not applicable.
Source: compiled during the evaluation

6.7 The assessment of bias in the individual trials does not adequately recognise important limitations associated with the indirect comparison analyses presented in

the re-submission. Trial 332 and the Biton 2005 and Berkovic 2007 trials were not exchangeable. There were differences across the trials in the clinical diagnosis of epilepsy, patients' ages, and standard care including the number and type of AEDs taken at baseline, which may have impacted upon the results of the indirect comparisons. Overall, there is a high risk of bias associated with the findings from the indirect comparisons in the re-submission.

6.8 Patients in Trial 332 and the Berkovic 2007 trial were diagnosed with IGE. It is unclear whether patients enrolled in Biton 2005 had IGE, although the publication of Biton 2005 appeared to indicate that the patients did have IGE. In addition, it is likely that the definition of IGE and diagnostic criteria for epilepsy have changed over time, and therefore may have differed between the older lamotrigine (Biton 2005) and levetiracetam (Berkovic 2007) trials and the newer perampanel trial (Trial 332)[i,ii].

6.9 The standard care (i.e. background AEDs) included in the trials is likely to have changed over time and be different across the trials, which will confound the indirect comparisons.

- There was a higher proportion of patients on inducer AEDs (enzyme-inducing) in the placebo arm compared to the perampanel arm (22% vs. 11%) in Trial 332. 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.
- Insufficient information was reported to enable a comparison of treatment arms within the Biton 2005 and Berkovic 2007 trials.

## *Comparative effectiveness*

6.10 The re-submission presented the results of Trial 332 for the direct comparison of perampanel plus standard care with placebo plus standard care. This is unchanged from the previous submission.

6.11 For the individual trials included in the indirect comparisons, the re-submission presented the percent change from baseline in the PGTC (or GTC in Berkovic 2007) seizure frequency in each treatment arm of each trial, during treatment (titration and maintenance) (Table 5).

i Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51(4):676-85.

ii Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1989;30(4):389-99.

**Table 5: PGTC or GTC seizure frequency, percent change from baseline, and differences between treatment arms in percent change during treatment (titration and maintenance)**

| Active drug (perampanel, lamotrigine, or levetiracetam) | | | | Placebo | | | | Median treatment difference[f] (95% CI) | P value[g] |
|---|---|---|---|---|---|---|---|---|---|
| n/N[b] (%) | Base-line[c] | Final[d] | % change from baseline[e] | n/N[b] (%) | Base-line[c] | Final[d] | % change from baseline[e] | | |
| **Trial 332: perampanel versus placebo** | | | | | | | | | |
| **Median[a]** | | | | | | | | | |
| 81/81 (100%) | 2.55 | 0.71 | -76.5% | 81/81 (100%) | 2.50 | 1.57 | -38.4% | -30.8% (-45.5%, -15.2%) | <0.0001 |
| **Mean (SD)[a]** | | | | | | | | | |
| 81/81 (100%) | 3.50 (2.62) | 1.90 (3.30) | -56.9% (50.8%) | 81/81 (100%) | 3.17 (2.00) | 2.87 (4.74) | -5.9% (184.6%) | NR | NR |
| **Biton 2005: lamotrigine versus placebo** | | | | | | | | | |
| **Median [a]** | | | | | | | | | |
| NR | 2.4 | 0.8 | -66.5 | NR | 2.9 | 2.0 | -34.2 | NR | 0.006 |
| **Mean (SD) [a]** | | | | | | | | | |
| NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Berkovic 2007: levetiracetam versus placebo** | | | | | | | | | |
| **Median[a]** | | | | | | | | | |
| 78/79 (99%) | 0.62 | 0.14 | -77.6 | 84/84 (100%) | 0.62 | 0.34 | -44.6 | -28.0 | <0.001 |
| **Mean (SD) [a]** | | | | | | | | | |
| 78/79 (99%) | 1.27 (2.46) | 0.55 | -56.5 | 84/84 (100%) | 1.20 (1.90) | 0.86 | -28.2 | -28.3 (-8.97, -47.64) | 0.004 |

[a] PGTC seizure frequency reported as 28 days in Trial 332; per month in Biton 2005; GTC seizure frequency reported as per week in Berkovic 2007. The outcome measure, percentage change from baseline and responder rate, are relative effects and therefore do not differ according to measurement period.

[b] n reporting data/N

[c] The median or mean number of PGTC or GTC seizures at pre-randomisation

[d] The median or mean number of PGTC or GTC seizures during the Titration and Maintenance Periods (combined)

[e] For the percent change in seizure frequency for PGTC or GTC seizures and all seizures the evaluation could not verify the median or mean percentage change in each treatment arm from the summary level data presented.

[f] The median treatment difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method

[g] Active drug versus placebo. The P value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomisation seizure frequency as a covariate.

CI = confidence interval; GTC = generalised tonic clonic; NR = not reported; PGTC = primary generalised tonic clonic; SD = standard deviation

Source: Table B.6.1, p103, of the re-submission

6.12 For the indirect comparisons, the re-submission presented the 50% PGTC or GTC seizure responder rate during the maintenance phase (Table 6).

**Table 6: Indirect comparisons: 50% PGTC or GTC seizure responder rate during the maintenance phase[a]**

| Trial type or estimate | Trial ID | n with event/N (%) | Common reference n with event/N (%) | Treatment effect OR (95% CI) | Treatment effect RR (95% CI) |
|---|---|---|---|---|---|
| Perampanel vs placebo | Trial 332[b] | 52/81 (64.2%) | 32/81 (39.5%) | 2.75 (1.45, 5.19) | 1.63 (1.19, 2.23) |
| Lamotrigine vs. placebo | Biton 2005 | 42/58 (72.4%) | 29/59 (49.2%) | 2.72 (1.26, 5.86) | 1.47 (1.09, 2.00) |
| Indirect comparison[c]: **Perampanel vs. lamotrigine** | – | – | – | 1.01 (0.37, 2.74) | 1.10 (0.71, 1.71) |
| Perampanel vs. placebo | Trial 332[b] | 52/81 (64.2%) | 32/81 (39.5%) | 2.75 (1.45, 5.19) | 1.63 (1.19, 2.23) |
| Levetiracetam vs. placebo | Berkovic 2007 | 54/79 (68.4%) | 37/84 (44.0%) | 2.74 (1.45, 5.21) | 1.55 (1.17, 2.06) |
| Indirect comparison[c]: **Perampanel vs. levetiracetam** | – | – | – | 1.00 (0.41, 2.47) | 1.05 (0.69, 1.60) |

[a] **Trial 332:** 50% responder rate was defined as the percentage of subjects experiencing a 50% or greater reduction in PGTC seizure frequency per 28 days in the Maintenance Period relative to baseline; **Biton 2005:** 50% responder rate was defined as the percentage of patients with a reduction of ≥50% in the frequency of PGTC seizures per month during the Maintenance Phases relative to the Baseline Phase; **Berkovic 2007:** 50% responder rate was defined as ≥50% reductions in the frequency of GTC seizures per week from the baseline period to the treatment period (evaluation)

[b] Full Analysis (FA) Set

[c] Indirect estimate of effect adjusted for the common reference.

– = not required; CI = confidence interval; n = number of participants with event; N = total number of participants in group; OR = odds ratio; RR = relative risk

Source: modified from Table B.6.4, p108, of the re-submission

6.13 The evaluation considered it difficult to draw any conclusion regarding the treatment effect of perampanel compared with either lamotrigine or levetiracetam, in terms of percent change in PGTC seizure frequency and 50% PGTC or GTC seizure responder rate, given the exchangeability issues as mentioned above.

6.14 The re-submission also presented indirect comparisons for the proportion of patients achieving seizure free status (PGTC seizures and all seizures) during the maintenance phase. As only very small numbers of patients achieved seizure free status, the 95% confidence intervals for the relative treatment effect were too wide to draw any reliable conclusions.

6.15 The evaluation noted that the re-submission did not provide non-inferiority margins for any of the outcomes in the indirect comparisons presented, and therefore the claim of non-inferiority cannot be assessed.

## *Comparative harms*

6.16 The safety data from Trial 332 presented in the re-submission is unchanged from the previous submission. It is noted that patients at high risk of suicide were excluded

from Trial 332. The US Food and Drug Administration (FDA) has stated[iii] 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.

6.17 A summary of overall adverse events in Trial 332 and the Biton 2005 and Berkovic 2007 trials is presented in Table 7.

**Table 7: Summary of overall adverse events in Trial 332 and the Biton 2005 and Berkovic 2007 trials**

| Category | Perampanel (N=81) n (%) | Placebo (N=82) n (%) | Lamotrigine (N=58) n (%) | Placebo (N=59) n (%) | Levetiracetam (N=79) n (%) | Placebo (N=84) n (%) |
|---|---|---|---|---|---|---|
| At least one TEAE | 67 (82.7%) | 59 (72.0%) | NR | NR | 57 (72.2%) | 57 (67.9%) |
| Treatment-related TEAEs | 56 (69.1%) | 37 (45.1%) | 13 (22%) | 6 (10%) | 31 (39.2%) | 25 (29.8%) |
| Serious TEAEs | 6 (7.4%) | 7 (8.5%) | NR | NR | 3 (3.8%) | 8 (9.5%) |
| Deaths | 1 (1.2%) | 1 (1.2%) | NR | NR | NR | NR |
| Other SAEs | 5 (6.2%) | 6 (7.3%) | NR | NR | NR | NR |
| TEAEs leading to study drug dose adjustment | 16 (19.8%) | 10 (12.2%) | NR | NR | NR | NR |
| TEAEs leading to study drug withdrawal | 9 (11.1%) | 5 (6.1%) | 5 (8.6%) | 2 (3.4%) | 1 (1.3%) | 4 (4.8%) |
| TEAEs leading to study drug dose reduction | 8 (9.9%) | 6 (7.3%) | NR | NR | NR | NR |
| TEAEs leading to study drug dose interruption | 1 (1.2%) | 0 | NR | NR | NR | NR |

NR = not reported; SAE = serious adverse event; TEAE = treatment emergent adverse event
Source: Table B.6.20, p129, of the re-submission

6.18 The re-submission presented indirect comparisons for the outcomes of at least one AE, at least one serious AE and an AE leading to study drug withdrawal. For the majority of these AEs, these analyses lacked adequate statistical power.

## *Benefits and harms*

6.19 The comparative benefits and harms for perampanel plus standard care versus placebo plus standard care were unchanged from the evaluation of the original submission, and the results can be found in Table 8.

[iii] FDA Centre for Drug Evaluation and Research Summary Review: Perampanel, 21 October 2012

**Table 8: 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)** |
| | | | | **Perampanel** | **PBO** | |
| 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 withdrawal | 9/81 | 5/82 | 1.82 (0.64, 5.20) | 11.1 | 6.1 | 5% (-4%, 14%) |

* 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

6.20 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 ≥ 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*

6.21 The re-submission described perampanel as superior in terms of comparative effectiveness and inferior in terms of comparative safety to placebo. This is unchanged from the previous submission.

6.22 The re-submission described perampanel as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety, to either lamotrigine or levetiracetam.

6.23 The PBAC considered that the claim of superior comparative effectiveness over placebo was reasonable; however, concerns remained about the appropriateness of this comparison and the number of patients who would use perampanel as a last line therapy.

6.24 The PBAC considered that the claim of inferior safety over placebo was reasonable.

6.25 The PBAC considered that on balance, the claim of non-inferior comparative effectiveness compared to either lamotrigine or levetiracetam may be reasonable. The PBAC noted that exchangability issues between the trials made it difficult to

draw accurate conclusions; however, it also noted that the co-administration of newer drugs in the perampanel trail compared to the lamotrigine or levetiracetam trials may bias agaianst perampanel.

6.26 The PBAC considered that the claim of non-inferior safety compared to either lamotrigine or levetiracetam was reasonable, but noted that the studies were not adequately powered to assess safety and that there is a need for longer term safety data.

## *Economic analysis*

6.27 The re-submission presented two economic evaluations:

- A cost-utility analysis of perampanel (plus standard care) vs. placebo (plus standard care). This approach was consistent with the clinical claim of superiority of perampanel compared with placebo; and
- A cost-minimisation analysis of perampanel (plus standard care) vs. other AEDs (plus standard care). This approach was consistent with the clinical claim of non-inferiority of perampanel compared with other AEDs.

Cost-utility analysis of perampanel versus placebo

6.28 The re-submission presented a modelled economic evaluation for perampanel compared with placebo. The model was the same as the one presented in the previous submission, except that the re-submission used an alternative source for health state utilities, and updated cost and mortality components to the most current estimates. A small change was also made to the transition probabilities from the '≤50% response' transition state.

6.29 The model structure and key drivers of the model were unchanged from the previous submission.

**Table 9: 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

**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 per year<br>13-52 annual seizures: 8.64 per year<br>53+ annual seizures: 10.16 per year | Moderate, increasing mortality risk associated with seizures favours perampanel |
| *Time Horizon* | *Longer time horizons associated with extrapolated data (the longest data source of clinical impact was 5 years)* | *High favours perampanel* |

Source: compiled during the evaluation

6.30 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 after 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. By year 6 (cycle 18), approximately 40% of the patients in the perampanel arm had failed treatment and had discontinued perampanel (reducing the average cost per cycle from $[redacted] to $[redacted]). 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 increased the ICER to $75,000/QALY – $105,000/QALY.

6.31 A number of previous PBAC concerns relating to the structure, application and extrapolation of treatment effect in the economic model remained outstanding and were not adequately addressed in the re-submission.

6.32 The results of the modelled evaluation are summarised below. These results must be interpreted with caution given the major structural issues identified with the model, and concerns relating to the application and extrapolation of treatment effect.

**Table 11: Results of the modelled economic evaluation of perampanel vs. placebo, as presented by the submissions**

| | Perampanel plus standard care | Standard care | Increment |
|---|---|---|---|
| **Modelled economic evaluation results – re-submission** | | | |
| Cost | $[redacted] | $[redacted] | $[redacted] |
| Number of seizures | 954 | 1,244 | 291 |
| LYG | 12.29 | 11.87 | 0.43 |
| QALY | 7.8 | 7.36 | 0.43 |
| ICER per Seizure Avoided | $[redacted] | | |
| ICER per LY | $[redacted] | | |
| ICER per QALY | $[redacted] | | |
| **Modelled economic evaluation results- July 2016 submission** | | | |
| Cost | $[redacted] | $[redacted] | $[redacted] |
| Number of seizures | 1,003 | 1,270 | 267 |
| LYG | 12.22 | 11.85 | 0.37 |
| QALY | 8.46 | 8.02 | 0.44 |
| ICER per Seizure Avoided | $[redacted] | | |
| ICER per LYG | $[redacted] | | |
| ICER per QALY gained | $[redacted] | | |

AED = Anti-epileptic drug; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life years.
Source: Table D.2.22, p211 of the re-submission and Table D.5.4, p125 Section D of the submission

6.33 The redacted table shows ICERs in the range of $45,000/QALY – $75,000/QALY.

6.34 The PSCR (p3-4) argued the outstanding concerns have been addressed, stating:

- Health states were defined to fit the trial information and published data;
- The baseline seizure frequency and response rate data were derived directly from Trial 332;
- Assuming no disease improvement after an increase in seizures is appropriate in a last-line model;
- The evaluators finding that 64% of patients are seizure-free at 5 years could not be verified by the sponsor;
- Transition probabilities in cycle 1 were based on trial data to month 4; and
- The model is internally valid.

6.35 The PBAC agreed with ESC that the submission sought to address some of the previous concerns raised by the committee in relation to the model, noting that:

- the model addressed the issue of double-counting the number of patients withdrawing seen in the previous submission; and
- the submission attempted to address the issue around utilities from the previous

submission as the utilities were derived from National Health and Wellness Survey data published by Gupta 2016, pertaining to epilepsy patients in five European countries. However, the ESC noted it is still unclear if this is representative of the Australian population. Additionally, the new utilities used in the model potentially lack face validity with a higher utility value for one seizure per week (0.634) compared with one seizure per month (0.627).

6.36 The ESC noted the model is very sensitive to the 40 year time horizon and considered that ten years would have been a more appropriate time horizon given the available data.

6.37 The ESC further noted the validation of the increased risk of mortality for epilepsy patients in different seizure health states by surveying eleven key opinion leaders did not substantially increase confidence in these estimates.

6.38 Overall the PBAC agreed with ESC that the submission did not adequately address the main structural issues previously identified with the model; however, it noted that there are difficulties associated with modelling epilepsy based on currently available data.

Cost-minimisation analysis of perampanel versus other AEDs

6.39 The equi-effective doses were estimated as perampanel 8mg/day, lamotrigine 300mg/day, levetiracetam 2000mg/day, topiramate 300mg/day and valproate 1500mg/day. The equi-effective dose for the comparators were based on the mid-point of the ranges of maintenance doses recommended from the respective product information (PI), which are identical to the therapeutic relativity of lamotrigine, levetiracetam and valproate for partial seizures; the PBAC has previously considered equi-effective doses of these drugs differ between partial seizures and PGTC seizures (November 2008 levetiracetam PSD).

6.40 The equi-effective doses of perampanel 8mg/day was the target maintenance dose specified in its PI and consistent with the target maintenance dose in Trial 332. Although the equi-effective dose of lamotrigine proposed in the re-submission (300mg/day) was similar to the mean dose of lamotrigine in Biton 2005 (296mg/day), the proposed equi-effective doses for levetiracetam (2000mg/day), topiramate (300mg/day) and valproate (1500mg/day) were not based on clinical evidence and the treatment effect of perampanel compared with these AEDs at the nominated doses is unknown.

6.41 In November 2008 when the PBAC considered levetiracetam for PGTC seizures, the PBAC accepted that lamotrigine 296mg/day (based on Biton 2005) is equi-effective to levetiracetam 2,887mg/day (based on Berkovic 2007) and topiramate 359mg/day. The equi-effective dose of valproate (compared to perampanel or any other AEDs) in the setting of PGTC seizures was not adequately explored in the re-submission and remains uncertain.

6.42 A summary of the average daily dose in the trials presented in Section B, maintenance doses in the respective PIs, the equi-effective doses of lamotrigine, levetiracetam and topiramate accepted by the PBAC in November 2008 and the equi-effective dose used in the re-submission is summarised in Table 12.

**Table 12: Summary of equi-effective doses from different sources**

| Drug | Adjunctive Treatment | Trials Presented in Section B | | Maintenance Dose in Product Information | PBS therapeutic relativity (partial seizures) | Nov. 2008 levetiracetam PSD, equi-effective dose (PGTC seizures) | Re-submission equi-effective dose |
|---|---|---|---|---|---|---|---|
| | | Trial target dose | Avg. Daily dose – trial | | | | |
| Lamotrigine (Biton 2005) | Taking valproate | 200mg | (n=15) 188.9 (23.4)* | 100-200mg | 300mg | 296mg | 300mg |
| | Taking enzyme-inducing AED | 400mg | (n=24) 393.0 (24.1)* | 200-400mg | | | |
| | Taking other | 300mg | (n=3) 233.3 (115.5)* | 100-200mg | | | |
| Levetiracetam | NA | 3000mg /day | NR | Therapeutic dose: 500mg twice daily Can be increased to 1500mg twice daily | 2000mg | 2887mg | 2000mg |
| Topiramate | | | | 200-400mg, maximum 1000mg | 300mg | 359mg | 300mg |
| Valproate | | | | 20-30mg/kg; 1300-2100mg/day ** | NR | NR | 1500mg |
| Perampanel | | 8mg | Mean=7.6mg^ Median=8mg^ | 8mg | | | 8mg |

NA= Not applicable; NR=Not Reported
*>12 year old sub-group
** based on average weight of 70.66kg, as per the perampanel trial.
^last daily dose, Table 14.3.1.1.9 of the perampanel CSR
Source: Compiled during the evaluation

6.43 The re-submission used a lower dose for levetiracetam and topiramate in the cost-minimisation analysis than the equi-effective dose accepted by the PBAC in November 2008 for levetiracetam and topiramate. Although the result of the cost-minimisation analysis is conservative using these lower doses, the treatment effect of perampanel 8mg/day compared with levetiracetam and topiramate at these doses is unknown. No comparative treatment effect of perampanel versus topiramate or valproate at any dose is presented in the re-submission.

6.44 The results of the cost-minimisation analysis, as presented in the re-submission are provided in Table 13.

**Table 13: Results of the cost-minimisation analysis as presented in the re-submission**

| Comparator (weight) | Steady-state dose | Assumed daily regimen | Ex-manufacturer price for maximum quantity | Daily ex-manufacturer cost | Perampanel: Ex-manufacturer price (28 x 8mg pack) |
|---|---|---|---|---|---|
| Lamotrigine (22.6%) | 300 mg | 3 x 100 mg | 56 × 100 mg = $[redacted] | $[redacted] | $[redacted] |
| Levetiracetam (36.8%) | 2000 mg | 2 x 1000 mg | 60 × 1000 mg = $[redacted] | $[redacted] | $[redacted] |
| Topiramate (10.3%) | 300 mg | 3 x 100 mg | 60 × 100 mg = $[redacted] | $[redacted] | $[redacted] |
| Valproate sodium (30.3%) | 1500 mg | 3 x 500 mg | 200 × 500 mg = $[redacted] | $[redacted] | $[redacted] |
| All comparators (100.0%) | | | | $[redacted] | $[redacted] |

Source: Table D.1.2, p186, Section D of the re-submission

6.45 The PSCR (p4) argued the relativities used in the submission were conservative.

6.46 The ESC noted that when compared with the trial based doses, the mid-point dose range used in the submission results in a lower cost per day for perampanel.

6.47 The respective proportion of lamotrigine, levetiracetam, topiramate, and valproate usage in the treatment of PGTC seizures was estimated from a survey of a limited number of epileptologists (14 respondents with 10 completions). Given the small number of respondents to these questions, heterogeneity in responses to each question, and the uncertain representativeness of the respondents to the Australian epilepsy treating clinicians, the results of the survey may not be applicable to Australian clinical practice.

6.48 The PSCR (p4) argued the PBS price for levetiracetam is now significantly lower than the price proposed in the submission for treatment of epilepsy with PGTC seizures which was recommended for listing by PBAC in November 2008. This is due to levetiracetam being an F2 and having taken multiple rounds of price disclosure.

Determination of the weighted price for perampanel

6.49 The results of both the cost-minimisation and cost-utility analyses were used to calculate a weighted ex-manufacturer price of 8mg perampanel. The proportion of expected use of perampanel as a substituted drug (perampanel vs. other AEDs), and as a last-line therapy (perampanel vs. placebo) were obtained from a survey of epileptologists conducted by the re-submission, and used to weight the proposed price of perampanel. As noted above, the evaluation considered that the results from the survey may not reflect Australian clinical practice.

6.50 The pre-PBAC Response argued that the survey included a significant proportion of the estimated 30-40 neurologists who wholly treat epilepsy across Australia (26 clinicians - 20 epileptologists and 6 paediatric neurologists) and that the response rate was high. It further noted that as the restriction requires perampanel treatment to be initiated by a neurologist that this sample is representative of those who would be initiating treatment in Australia.

6.51 The PBAC agreed with its ESC that the survey of epileptologists is likely to give an overestimate of the proportion of 'last line substitution'. The PBAC considered that the proportion of perampanel use in last-line vs earlier line treatment should be 30-40% and 60-70% respecitively.[iv]

6.52 The submission's proposed weighted price of perampanel is summarised in Table 14.

**Table 14: Weighted price of perampanel**

| Setting | Proportion of perampanel use | Ex-manufacturer Price of perampanel 8mg/day |
|---|---|---|
| Last line (versus placebo) | 76.1%^ | $[redacted]* |
| Earlier line (versus other AEDs) | 23.9%^ | $[redacted]** |
| Weighted | | $[redacted] |

^based on clinician survey (14 respondents with 10 completions)
*The re-submission proposed price used in the cost-utility analysis of perampanel compared with placebo
**weighted price of perampanel derived from cost-minimisation analysis (perampanel versus lamotrigine, levetiracetam, topiramate and valproate)
Source: compiled during the evaluation.

## *Drug cost/patient/year: $[redacted] ex-manufacturer*

6.53 The re-submission proposed an ex-manufacturer price for perampanel of $[redacted]/day (8 mg/day), based on a weighted comparator approach (76.1% of perampanel use in the last line setting compared with placebo and 23.9% as an earlier line of treatment compared with other AEDs). Patients responding to perampanel would be expected to continue taking perampanel indefinitely due to the chronic nature of the disease. This is compared with a daily ex-manufacturer cost of $[redacted] if other AEDs are the only comparators (weighted daily costs of lamotrigine, levetiracetam, topiramate and valproate).

6.54 The previous submission proposed a daily dispensed price of $[redacted], based on a dispensed price for maximum quantity (DPMQ) of $[redacted] for a pack of 28 tablets.

## *Estimated PBS usage & financial implications*

6.55 This re-submission is not being considered by DUSC.

6.56 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 IGE and PGTC seizures who have failed treatment with at least two AEDs.

[iv] Laxer, K.D., Trinka, E., Hirsch, L.J., et al (2014) The consequences of refractory epilepsy and its treatment. *Epilepsy and Behaviour,* pp 59-70.

**Table 15: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | |
| Patients who would add perampanel to last-line therapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients who would use perampanel instead of other AEDs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total number of patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Number of scripts dispensed | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated financial implications of perampanel** | | | | | |
| Cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Co-payments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost to PBS/RPBS less co-payments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated financial implications for other AEDs** | | | | | |
| Cost to PBS/RPBS (including patient co-payments) | | | | | |
| Lamotrigine | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Levetiracetam | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Topiramate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Valproate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total cost to PBS/RPBS (including patient co-payments) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total co-payments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cost to PBS/RPBS less co-payments | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net financial implications –re-submission** | | | | | |
| Net costs to PBS/RPBS (patient co-payments removed) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net costs to MBS (15% patient co-payments removed)[a] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Overall net cost to Federal Government | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Change in other HRU costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Overall net cost to combined government health budgets | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net financial implications – July 2016 submission** | | | | | |
| Net cost to PBS/RPBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net cost to other government budgets | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Net cost to PBS/RPBS/MBS | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[a] Adjusted for continuous uptake
[b] Assuming average of 15 scripts per year as estimated by the re-submission.
[c] MBS costs associated with general practitioner/specialist visit
[d] Costs for hospitalisation and emergency department visit
HRU = healthcare resource utilisation
Source: Table E.2.2 to Table E.2.10, Table E.3.3, Table E.3.4 and Table E.5.5 of the re-submission and Fycompa PGTC_Section E FINAL.xksx, from the original submission.

6.57 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.

6.58 The number of patients eligible for treatment with perampanel may not be as predicted in the re-submission. The prevalence rate of epilepsy was estimated form D'Souza which was substantially lower than that estimated in the ABS National

Health Survey and may therefore be underestimated. This parameter remains unchanged from the previous submission.

6.59 The estimated proportion of PGTC patients eligible for treatment with perampanel, and the expected treatment uptake rate was estimated based on the results of a clinician survey (described above) and remain highly uncertain.

6.60 The PSCR (p4-5) stated the sponsor is willing to enter into a risk share arrangement with the Department which caps the number of patients treated under the PBS to reduce the uncertainty around patient numbers.

6.61 The PBAC noted that the financial estimated presented by the submission would need to be recalculated to take into account the basis upon which the PBAC has recommended listing.

## *Quality Use of Medicines*

6.62 The sponsor stated that it has implemented a Pharmacovigilance and risk-management plan within the Australian Specific Annex (ASA) to the TGA to enhance the quality use of perampanel for the treatment of patients with IGE-PGTC. The re-submission stated that a number of other activities will occur in order to support the quality use of medicines, including a 'Dear Healthcare Professional' (HCP) letter to announce the availability of perampanel for this indication, development and distribution of a patient booklet in lay language, development of a dosing guidance card for prescribing HCP, and development of a larger format Product Information Booklet for HCPs. The previous submission did not provide any information on the quality use of medicines.

## *Financial Management – Risk Sharing Arrangements*

6.63 Perampanel is currently PBS listed for partial – onset (or focal) epilepsy and a price-volume based risk-share arrangement exists in conjunction with UCB Biosciences (lacosamide – Vimpat). This is encompassed within a Commonwealth Deed which is intended to expire on 1st April 2020. The sponsor is willing to undertake a separate price-volume, risk-share arrangement for IGE-PGTC. The re-submission stated that the most appropriate mechanism would be an annual cap based trigger for a further price reduction based on the finalised figures within the financial estimates and budgetary implications contained in section E of the re-submission. The previous submission did not propose any risk-sharing arrangements. The PBAC, noting the uncertainty around patient numbers, recommended that a risk share which caps the number of patients treated with perampanel for IGE-PGTC under the PBS (as proposed in the PSCR), is appropriate.

# 7 PBAC Outcome

7.1 The PBAC recommended the listing of perampanel for the treatment of primary generalised tonic-clonic (PGTC) seizures in patients with idiopathic generalised epilepsy (IGE), on the basis of a mixed comparison against placebo in refractory patients who have failed to respond adequately to other anti-epileptic drugs (AED); and against other AEDs (valproate, lamotrigine, levetiracetam and topiramate) for refractory patients in whom perampanel will substitute for another AED.

7.2 The PBAC noted the comments in the sponsor hearing and clinician statement and agreed that there was a clinical need for an additional treatment option for patients with PGTC seizures.

7.3 The PBAC did not agree that the calculation of the weighted price presented in the submission was appropriate. The committee noted that the proposed proportion of the comparators was derived from the results of a survey that may not be valid; and that the weighted comparator price results in a significantly higher price for perampanel vs. cost-minimisation against currently listed AEDs alone. The PBAC considered (citing Laxer, K.D. *et al* (2014)[v]) that the proportion of patients using perampanel last-line was overestimated and that the proportion of perampanel use in last-line vs earlier line treatment was more likely to be 30-40% and 60-70% respectively (vs. 76.1% and 23.9% respectively). The PBAC noted that the ex-manufacturer price per day of perampanel, if recalculated on this basis would be between $[redacted] and $[redacted] rather than the $[redacted] requested by the submission.

7.4 The PBAC noted that the proposed restriction had been revised to allow earlier treatment with perampanel (i.e. as an additional option for refractory patients, rather than last-line only) consistent with its earlier advice.

7.5 The PBAC noted that the equi-effective doses were nominated as perampanel 8 mg/day, lamotrigine 300 mg/day, levetiracetam 2000 mg/day, topiramate 300 mg/day and valproate 1500 mg/day. The PBAC considered there was uncertainty around the equi-effective doses but that overall these doses provided a reasonable basis for the cost-minimisation analysis.

7.6 The PBAC recalled that in its consideration of perampanel in July 2016 it considered that a comparison against placebo was not appropriate – noting that the clinical place of therapy should be as an additional option to those currently available for the treatment of refractory patients. The PBAC maintained the view that a comparison wholly against placebo was not appropriate. However, on balance – noting the clinical need for another therapeutic option in refractory patients – the committee pragmatically considered the approach of a mixed comparison against placebo for patients who have failed to respond adequately to existing treatment

[v] Laxer, K.D., Trinka, E., Hirsch, L.J., et al (2014) The consequences of refractory epilepsy and its treatment. *Epilepsy and Behaviour,* pp 59-70.

options and against other currently available AEDs (valproate, lamotrigine, levetiracetam and topiramate) for patients in whom perampanel will substitute for another AED is acceptable - subject to changes to the proportion of patients in each comparator group as discussed in paragraph 7.3.

7.7 The PBAC considered that the claim of superior comparative effectiveness and inferior safety compared to placebo was reasonable.

7.8 The committee noted that there were significant exchangeability issues between the trials which made it difficult to draw accurate conclusions regarding non-inferiority of perampanel to lamotrigine or levetiracetam. These included: differences in the clinical diagnosis of epilepsy and standard of care; the number of AEDs taken at baseline; and differences in the common reference (placebo) arms observed across the trials for a number of efficacy and safety outcomes which made However, the committee also noted that that the use of newer drugs in the lamotrigine or levetiracetam trials may bias against perampanel and that on balance, the claim of non-inferior comparative effectiveness was reasonable.

7.9 The PBAC considered that the claim of non-inferior safety compared to either lamotrigine or levetiracetam was reasonable, but noted that the studies were not adequately powered to assess safety and that there is a need for longer term safety data.

7.10 The PBAC considered that there were a number of outstanding issues with the economic analysis presented that had not been addressed. These included concerns with respect to structure, application and extrapolation of treatment effect. However, the committee also noted that there are difficulties associated with modelling epilepsy based on currently available data and the sponsors comment that any resubmission would be unlikely to address the uncertainty any further.

7.11 The PBAC considered that the number of patients estimated to be eligible for treatment with perampanel is likely to be an underestimate, noting that the prevalence rates of epilepsy and the proportion of patients with PGTC seizures who are eligible for treatment with perampanel may both be underestimated.

7.12 The PBAC recommended that perampanel should not be treated as interchangeable with any other drugs.

7.13 The PBAC advised that perampanel is suitable for prescribing by nurse practitioners as continuing therapy only.

7.14 The PBAC recommended that the Early Supply Rule should apply.

7.15 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

**Outcome:**
Recommended

# 8 Recommended listing

## 8.1 Add new item:

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Proprietary Name and Manufacturer | |
|---|---|---|---|---|
| PERAMPENAL<br>2 mg tablet, 7 | 2 | 1 | Fycompa® | Eisai Australia Pty Ltd |

| | |
|---|---|
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | ☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives |
| **Severity:** | Primary generalised tonic-clonic seizures |
| **Condition:** | Idiopathic generalised epilepsy |
| **PBS Indication:** | Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures |
| **Treatment phase:** | Initial |
| **Restriction Level / Method:** | ☐ Restricted benefit<br>☐ Authority Required - In Writing<br>☐ Authority Required - Telephone<br>☐ Authority Required - Emergency<br>☐ Authority Required - Electronic<br>☒ Streamlined |
| **Treatment criteria:** | Must be treated by a neurologist |
| **Clinical criteria:** | The condition must have failed to be controlled satisfactorily by at least two anti-epileptic drugs,<br><br>AND<br><br>The treatment must be in combination with at least one PBS subsidised anti-epileptic drug,<br><br>AND<br><br>The treatment must be for dose titration purposes |
| **Population criteria:** | Patient must be aged 12 years or older. |
| **Administrative Advice** | No-increase to the maximum quantities will be authorised. |

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Proprietary Name and Manufacturer | |
|---|---|---|---|---|
| PERAMPENAL | | | | |
| 4 mg tablet, 28 | 1 | 2 | Fycompa® | Eisai Australia Pty Ltd |
| 6 mg tablet, 28 | 1 | 2 | | |
| 8 mg tablet, 28 | 1 | 5 | | |
| 10 mg tablet, 28 | 1 | 5 | | |
| 12 mg tablet, 28 | 1 | 5 | | |

| | |
|---|---|
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | ☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives |
| **Severity:** | *Primary generalised tonic-clonic seizures* |
| **Condition:** | Idiopathic Generalised epilepsy |
| **PBS Indication:**<br><br>*PBS Indication is the combination of the Episodicity, Severity and Condition.* | Idiopathic generalised epilepsy with primary generalised tonic-clonic seizures |
| **Treatment phase:** | Continuing |
| **Restriction Level / Method:** | ☐ Restricted benefit<br>☐ Authority Required - In Writing<br>☐ Authority Required - Telephone<br>☐ Authority Required - Emergency<br>☐ Authority Required - Electronic<br>☒ Streamlined |
| **Clinical criteria:** | Patient must have previously been issued with an authority prescription for this drug |
| **Population criteria:** | Patient must be aged 12 years or older. |
| **Administrative Advice** | No-increase to the maximum quantities will be authorised.<br><br>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. |

# 9 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.

## 10 Sponsor's Comment

The sponsor had no comment.