

5.12 PERAMPANEL, 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 major submission sought an Authority required (STREAMLINED) listing for adjunctive treatment of partial epilepsy in refractory patients aged 12 years and older.

2 Requested listing

- 2.1 The following listing with an 'initial treatment' listing for the 2 mg (14 tablets) strength and a 'continuing treatment' listing for the 4 mg and higher strengths was sought:

| Name, Restriction, Manner of administration and form | Max. Qty (Packs) | No. of Rpts | DPMQ |
|--|------------------|-------------|---------|
| PERAMPANEL perampanel 2 mg tablet, 7 | 2 | 1 | \$52.50 |

| |
|--|
| <p>Authority required (STREAMLINED) Intractable partial epileptic seizures</p> <p>Treatment Phase: Initial</p> <p>Clinical criteria: The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent, AND</p> <p>The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents, AND</p> <p>The treatment must be for dose titration purposes (2 mg, 7 packs sizes only)</p> <p>Population criteria: Patient must be aged 12 years or older.</p> <p>Treatment criteria Must be treated by a neurologist</p> |
|--|

| Name, Restriction, Manner of administration and form | Max. Qty (Packs) | No. of Rpts | Dispensed Price for Max. Qty |
|--|------------------|-------------|------------------------------|
| PERAMPANEL perampanel 4 mg tablet, 28 | 1 | 5 | \$188.67 |
| perampanel 6 mg tablet, 28 | 1 | 5 | \$272.87 |
| perampanel 8 mg tablet, 28 | 1 | 5 | \$355.59 |
| perampanel 10 mg tablet, 28 | 1 | 5 | \$355.59 |
| perampanel 12 mg tablet, 28 | 1 | 5 | \$355.59 |

Authority required (STREAMLINED)

Intractable partial epileptic seizures

Treatment Phase:

Continuing

Clinical criteria:

Patient must have previously been treated with PBS-subsidised perampanel.

Population criteria:

Patient must be aged 12 years or older.

Administrative advice:

Note:

No applications for increased maximum quantities will be authorised.

Note:

Continuing Therapy Only:

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.

- 2.2 Listing was sought on a cost-minimisation basis with lacosamide.

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

3 Background

- 3.1 Perampanel was TGA registered on 23 May 2014 for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

The submission was made under TGAPBAC Parallel Process provisions.

- 3.2 This was the first consideration by the PBAC for perampanel.

4 Clinical place for the proposed therapy

- 4.1 The submission positioned perampanel as an alternative option to lacosamide for the adjunctive treatment of intractable partial epilepsy.

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

5 Comparator

- 5.1 The submission nominated lacosamide. This was the appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

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

Clinical trials

6.3 In the absence of head-to-head trials, the submission presented an indirect comparison of perampanel and lacosamide using placebo as the common comparator. The trials were of sufficient comparability to inform an indirect comparison.

6.4 A list of the trials presented in the submission is shown in the table below.

Trials (and associated reports) presented in the submission

| Trial ID/First Author | Protocol/Publication Title | Citation |
|-------------------------------|---|---------------------------------------|
| Perampanel vs. placebo | | |
| Trial 304 | A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures. | 2011 |
| Krauss | Adjunctive perampanel for refractory partial-onset seizures: Randomized phase III study 304. | <i>Neurology</i> 2012; 79: 589-596 |
| Trial 305 | A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures. | 2011. |
| Krauss | Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. | <i>Epilepsia</i> 2013; 54(1): 117-125 |
| Trial 306 | A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures. | 2011. |
| Krauss | Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. | <i>Neurology</i> 2012; 78: 1408–1415 |

| | | |
|-------------------------------|---|---------------------------------------|
| Lacosamide vs. placebo | | |
| Ben-Menachem | Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. | <i>Epilepsia</i> 2007; 48(7):1308-17. |
| Chung | Lacosamide as adjunctive therapy for partial-onset seizures: A randomised controlled trial. | <i>Epilepsia</i> 2010; 51(6):958-67. |
| Halasz | Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. | <i>Epilepsia</i> 2009;50(3):443-53. |

Source: Table 6 B.2.3, p43 of the submission

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

Comparative effectiveness

6.5 The table below provides a summary of the indirect comparison results.

Summary of results of the indirect comparison: 50% reduction in 28-day seizure frequency in the overall patient population

| Variable | Active Treatment n/N (%) | Placebo n/N (%) | RR (95% CI) | RD% (95% CI)* |
|---|-----------------------------|--------------------|-------------|---------------|
| Perampanel 4 mg | 49/172 (28.49) | 33/184 (17.93) | 1.59 | 10.55 |
| Lacosamide 200 mg | 91/267 (34.08) | 62/255 (20.39) | 1.40 | 9.87 |
| Indirect comparison: perampanel 4 mg vs lacosamide 200 mg | | | 1.14 | 0.68 |
| Perampanel 8 mg | 152/431 (35.27) | 85/441 (19.27) | 1.80 | 16.01 |
| Lacosamide 400 mg | 185/466 (39.70) | 81/359 (22.56) | 1.77 | 17.89 |
| Indirect comparison: perampanel 8 mg vs lacosamide 400 mg | | | 1.02 | -1.88 |
| Perampanel 12 mg | 89/254 (35.04) | 52/257 (20.23) | 1.74 | 14.71 |
| Indirect comparison: perampanel 12 mg vs lacosamide 400 mg | | | 0.98 | -3.18 |

* Estimated during the evaluation using StatsDirect: Version 2.7.8; Results in bold indicate RRs or RDs that are statistically significant
Abbreviations: CI = confidence interval; n = number with event; N = number in group; RD = risk difference; RR = relative risk
Source: Table 22 B.6.1, p76-77 of the submission

6.6 Results of the indirect comparison for the outcome of seizure freedom in the overall patient population showed no statistically significant difference between perampanel 4 mg and lacosamide 200 mg, perampanel 8 mg and lacosamide 400 mg, and perampanel 12 mg and lacosamide 400 mg, when placebo was used as the common comparator.

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

Comparative harms

6.7 The analysis of comparative harms for perampanel and lacosamide was limited as only an indirect comparison of treatment emergent adverse events (TEAEs) occurring in ≥10% of patients was possible. From this analysis it was determined that there was no statistically significant difference between perampanel and lacosamide for the analysed TEAEs (dizziness, somnolence, headache, fall, irritability, ataxia and fatigue). It was observed from the clinical study reports for Trial 304 and Trial 306 that an increased incidence of aggression and psychiatric disorders occurred in the perampanel treatment arms compared to placebo. In Trial 304, a statistically significant increased risk of aggression was observed for the comparison of perampanel 12 mg and placebo (RR = 13.56, 95% CI: 1.68, infinity). In Trial 306, there was a statistically significantly increased risk of psychiatric disorders for the comparison of perampanel 8 mg and placebo (RR = 1.88, 95% CI: 1.02, 3.47).

6.8 It was noted that the ACPM advised that the finalised Product Information of perampanel should address a caution for use in patients with psychosis and a separate caution for use in patients aged 65 and over relating to the increased frequency of dizziness and falls.

6.9 A summary of the comparative benefits and harms for perampanel versus lacosamide is presented in the table below.

Summary of comparative benefits and harms for perampanel and lacosamide

| | PER | PBO | LCS | RR (95% CI) | Event rate/100 patients* | | | RD% (95% CI) |
|---|--------|--------|--------|-------------|--------------------------|-------|-------|--------------|
| | | | | | PER | PBO | LCS | |
| Benefits | | | | | | | | |
| 50% reduction in 28-day seizure frequency in the overall patient population: indirect comparison | | | | | | | | |
| PER 4 mg | 49/172 | 33/184 | - | 1.59 | 28.49 | 17.93 | - | 10.55 |
| LCS 200 mg | - | 62/255 | 91/267 | 1.40 | - | 20.39 | 34.08 | 9.87 |

| | | | | | | | | |
|--|---------|--------|--------------|--------------------------|-------|--------------|-------|--------------|
| Indirect comparison: PER 4 mg vs LCS 200 mg | | | | 1.14 | - | - | | 0.68 |
| PER 8 mg | 152/431 | 85/441 | - | 1.80 | 35.27 | 19.27 | - | 16.01 |
| LCS 400 mg | - | 81/359 | 185/466 | 1.77 | - | 22.56 | 39.70 | 17.89 |
| Indirect comparison: PER 8 mg vs LCS 400 mg | | | | 1.02 | - | | -1.88 | |
| Harms: perampanel vs lacosamide | | | | | | | | |
| Dizziness | | | | | | | | |
| PER 4 mg | 28/172 | 18/185 | - | 1.67 | 16.28 | 9.73 | - | 6.55 |
| LCS 200 mg | - | 18/260 | 43/270 | 2.26 | - | 6.92 | 15.93 | 8.79 |
| Indirect comparison: PER 4 mg vs LCS 200 mg | | | | 0.74 | - | | -2.24 | |
| PER 8 mg | 137/431 | 40/442 | - | 3.44 | 31.79 | 9.05 | - | 22.76 |
| LCS 400 mg | - | 29/364 | 139/471 | 3.25 | - | 7.97 | 29.51 | 19.17 |
| Indirect comparison: PER 8 mg vs LCS 400 mg | | | | 1.06 | - | | 3.59 | |
| Somnolence | | | | | | | | |
| PER 4 mg | 16/172 | 12/185 | - | 1.43 | 9.30 | 6.49 | - | 2.82 |
| LCS 200 mg | - | 6/97 | 8/107 | 1.21 | - | 6.19 | 7.48 | 1.29 |
| Indirect comparison: PER 4 mg vs LCS 200 mg | | | | 1.18 | - | | 1.53 | |
| PER 8 mg | 67/431 | 32/442 | - | 2.17 | 15.55 | 7.24 | - | 8.50 |
| LCS 400 mg | - | 13/201 | 34/312 | 1.70 | - | 6.47 | 10.90 | 4.48 |
| Indirect comparison: PER 8 mg vs LCS 400 mg | | | | 1.28 | - | | 4.02 | |
| Harms: perampanel vs. placebo | | | | | | | | |
| | PER | PBO | RR (95% CI) | Event rate/100 patients* | | RD% (95% CI) | | |
| | | | | PER | PBO | | | |
| Aggression; PER 12 mg | 7/134 | 0/121 | 13.56 | 5.22 | 0.00 | 5.22 | | |
| Psychiatric disorders; PER 8 mg [^] | 24/169 | 14/185 | 1.88 | 14.20 | 7.56 | 6.63 | | |

* Duration of exposure: perampanel Trials 304, 305 and 306 = 19 weeks; lacosamide trials Ben-Menachem 2007 and Chung 2010 = 18 weeks, Halasz 2009 = 16 weeks; Trial 306 Results in **bold** indicate RRs or RDs that are statistically significant. Abbreviations: LCS = lacosamide; PER = perampanel; PBO = placebo; RD = risk difference; RR = risk ratio. Source: Compiled during the evaluation

- 6.10 It was noted that on the basis of the indirect evidence presented by the submission, perampanel and lacosamide are comparable in effectiveness and safety.
- 6.11 In terms of effectiveness, when compared to placebo, the addition of either of these drugs to an existing anti-epileptic drug regime will reduce seizure frequency.
- 6.12 On the basis of indirect evidence, for every 100 patients treated with perampanel 8 mg, compared to placebo:
- Approximately 16 additional patients would achieve the outcome of a 50% reduction in 28 day seizure frequency.
- 6.13 On the basis of indirect evidence, for every 100 patients treated with lacosamide 400 mg, compared to placebo:
- Approximately 18 additional patients would achieve the outcome of a 50% reduction in 28 day seizure frequency,

- 6.14 In terms of safety, when compared to placebo, both of these drugs are associated with side-effects. Treating 4 patients with 8 mg of perampanel or 5 patients with 400 mg of lacosamide is associated with one additional patient developing dizziness. Treating 12 patients with 8 mg of perampanel or 22 patients with 400 mg of lacosamide is associated with one additional patient developing sleepiness over 16 to 19 weeks.
- 6.15 In addition, on the basis of direct evidence, for every 100 patients treated with perampanel, compared to placebo:
- Approximately 5 additional patients would experience aggression with perampanel 12 mg over 19 weeks; and
 - Approximately 7 additional patients would experience psychiatric disorders with perampanel 8 mg over 19 weeks.
- 6.16 It was noted that there are no data available on these side-effects for lacosamide.

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

Clinical claim

- 6.17 The submission claimed non-inferiority between perampanel and lacosamide in terms of comparative effectiveness and comparative safety in patients with treatment-refractory partial epilepsy.
- 6.18 On the basis of the indirect evidence presented by the submission, the ESC considered that perampanel is non inferior compared to lacosamide in terms of comparative effectiveness and safety in patients with treatment-refractory partial epilepsy.

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

Economic analysis

- 6.19 The submission presented a cost-minimisation analysis based on the claim of non-inferiority of perampanel compared to lacosamide.
- 6.20 The equi-effective doses of perampanel were estimated as a daily dose relativity of perampanel to lacosamide of 1:50. The equi-effective doses were appropriately derived from the steady-state doses seen in the clinical trials. Once daily dosing of perampanel 2 mg, 4 mg, 6 mg and 8 mg is equal to twice-a-day dosing of lacosamide 50 mg, 100 mg, 150 mg and 200 mg respectively. Perampanel 10 mg and 12 mg was priced at the same level as perampanel 8 mg.
- 6.21 The table below shows the proposed prices:

Proposed PBS price for perampanel tablets - perampanel:lacosamide dose relativity = 1:50

| Perampanel | | | | Ex-man/day | Lacosamide | | | |
|------------|---------|----------|----------|------------|------------|----------|---------|----------|
| Dose/day | Tablets | DPMQ | Ex-man | | Ex-man | DPMQ | Tablets | Dose/day |
| 2 mg | 14 | \$52.50 | \$38.48 | \$2.75 | \$19.24 | \$30.42 | 14 | 100 mg |
| 4 mg | 28 | \$188.67 | \$153.92 | \$5.50 | \$153.92 | \$188.67 | 56 | 200 mg |
| 6 mg | 28 | \$272.87 | \$230.88 | \$8.25 | \$230.88 | \$272.87 | 56 | 300 mg |
| 8,10,12 mg | 28 | \$355.59 | \$307.81 | \$10.99 | \$307.81 | \$355.59 | 56 | 400 mg |

Abbreviations: DPMQ = Dispensed Price Maximum Quantity, Ex-man = ex-manufacturer price; PTP = price to pharmacist
Source: Table 32, p104 of the submission

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

Estimated PBS usage & financial implications

6.22 This submission was not considered by DUSC.

6.23 The likely number of prescriptions dispensed per year was estimated in the submission to be █████ in Year 5, at an estimated net cost per year to the PBS of \$█████ in Year 5. The submission’s estimates of PBS usage and financial implications are summarised in the table below:

| Estimated use and financial implications* | | | | | |
|--|----------------|----------------|----------------|----------------|----------------|
| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
| Estimated extent of use | | | | | |
| Market share | █████ % | █████ % | █████ % | █████ % | █████ % |
| Scripts | █████ | █████ | █████ | █████ | █████ |
| Estimated changes in cost of listing perampanel | | | | | |
| Net costs for perampanel | \$█████ | \$█████ | \$█████ | \$█████ | \$█████ |
| Substitution from lacosamide | \$█████ | \$█████ | \$█████ | \$█████ | \$█████ |
| Estimated net cost to PBS | \$█████ | \$█████ | \$█████ | \$█████ | \$█████ |

* Note: During the evaluation the financial estimates were updated to reflect the most recent ABS Australian population projections (ABS 3222.0 Series B, 2013). Source: Excel workbook ‘5. Appendix 5 EISAI_perampanel_Section E_Financial implications.xlsx’ provided with the electronic submission

6.24 The submission’s estimate of the cost of listing perampanel was most likely underestimated as the base case assumptions did not consider:

- Patients aged 12-15 years old, patients intolerant of lacosamide and patients previously considered unsuitable for further pharmacotherapy (i.e. considered for surgery) who may be eligible for perampanel; and
- Possible substitution of perampanel for second-line adjunctive AEDs other than lacosamide.

7 PBAC Outcome

7.1 The PBAC recommended listing perampanel as an Authority required (STREAMLINED) listing for the treatment of intractable partial epileptic seizures in patients meeting certain criteria on a cost-minimisation basis compared with lacosamide. The equi-effective doses were determined to be:

- perampanel 2 mg once daily is equi-effective to lacosamide 50 mg twice daily;
- perampanel 4 mg once daily is equi-effective to lacosamide 100 mg twice daily;
- perampanel 6 mg once daily is equi-effective to lacosamide 150 mg twice daily;
- perampanel 8 mg once daily is equi-effective to lacosamide 200 mg twice daily;
- perampanel 10 mg once daily is equi-effective to lacosamide 200 mg twice daily;
- perampanel 12 mg once daily is equi-effective to lacosamide 200 mg twice daily

7.2 The PBAC noted that the submission’s requested listing was intended to target the same population as lacosamide but that perampanel’s TGA registered indication limits treatment to patients from 12 years of age or over, while lacosamide’s TGA registered indication limits treatment to patients aged 16 years or over. The PBAC would welcome additional data on the use of these products in children. Apart from this difference, the PBAC agreed that the intent of perampanel’s restriction should be consistent with lacosamide’s restriction, including a streamlined Authority listing.

7.3 The PBAC accepted lacosamide as the appropriate comparator.

- 7.4 Based on the results of the indirect comparison of perampanel to lacosamide using placebo as the common comparator, the PBAC noted that there was no statistically significant difference in freedom from seizures (measured by observing the number of patients with a 50% reduction in their seizure frequency in a period of 28 days) observed between perampanel 4 mg and lacosamide 200 mg, perampanel 8 mg and lacosamide 400 mg, and perampanel 12 mg and lacosamide 400 mg.
- 7.5 In terms of safety, the PBAC noted the Product Information's caution on perampanel's use in patients aged 65 and an increased frequency of dizziness and falls, as well as the caution about patients with psychosis and increased risk of aggression. The PBAC noted that the Periodic Safety Update Report (PSUR) of September 2013 outlined no new emerging safety issues. The PBAC further noted a German observational study (Steinhoff 2014) (n=281) showing no significant changes in safety.
- 7.6 Based on the results of the indirect comparison and safety data presented, the PBAC accepted the submission's claim of non-inferiority between perampanel and lacosamide in terms of comparative effectiveness and comparative safety in patients with treatment-refractory partial epilepsy. As the PBAC accepted the clinical claim of non-inferiority to lacosamide, the submission's cost-minimisation approach to the economic analysis was appropriate.
- 7.7 The PBAC considered that it was reasonable to price perampanel 10 mg and 12 mg at the same level as perampanel 8 mg. The PBAC further noted that a risk share agreement currently applies to lacosamide and given that perampanel's proposed listing aims to cover the same patient population (with the exception of the slight difference in patient age eligibility), the PBAC recommended that perampanel be included in the same risk share agreement as lacosamide, adjusted for the slightly increased patient population.
- 7.8 The PBAC recommended that perampanel should not be treated as interchangeable on an individual patient basis with lacosamide or any other anti-epileptic drug as it considered that perampanel is likely to have a different side-effect profile to these other drugs.
- 7.9 The PBAC recommended that perampanel is suitable for prescribing by nurse practitioners as continuing therapy only.
- 7.10 The PBAC recommended that the Safety Net 20 Day Rule should not apply given the dose titration requirements in initiating therapy and given that it does not currently apply to other currently PBS-listed drugs for epilepsy.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new items:

Public Summary Document– July 2014 PBAC Meeting

| Name, Restriction, Manner of administration and form | Max. Qty (Packs) | No.of Rpts | Proprietary Name and Manufacturer | |
|---|---------------------|---------------|--------------------------------------|-------|
| PERAMPANEL | | | | |
| perampanel 2 mg tablet, 7 | 2 | 1 | Fycompa | Eisai |

| | |
|----------------------------|--|
| Category/Program | GENERAL- General Schedule (Code GE) |
| Episodicity: | --- |
| Severity: | Intractable |
| Condition: | partial epileptic seizures |
| Indication: | Intractable partial epileptic seizures |
| Treatment phase: | Initial treatment |
| Restriction: | Authority required (STREAMLINED) |
| Treatment criteria: | Must be treated by a neurologist |
| Clinical criteria: | The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent AND The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents |

| Name, Restriction, Manner of administration and form | Max. Qty (Packs) | No.of Rpts | Proprietary Name and Manufacturer | |
|---|---------------------|---------------|--------------------------------------|-------|
| PERAMPANEL | | | | |
| perampanel 4 mg tablet, 28 | 1 | 5 | Fycompa | Eisai |
| perampanel 6 mg tablet, 28 | 1 | 5 | Fycompa | Eisai |
| perampanel 8 mg tablet, 28 | 1 | 5 | Fycompa | Eisai |
| perampanel 10 mg tablet, 28 | 1 | 5 | Fycompa | Eisai |
| perampanel 12 mg tablet, 28 | 1 | 5 | Fycompa | Eisai |

| | |
|------------------------------|---|
| Category/Program | GENERAL – General Schedule (Code GE) |
| Episodicity: | --- |
| Severity: | Intractable |
| Condition | partial epileptic seizures |
| Indication: | Intractable partial epileptic seizures |
| Treatment phase: | Continuing treatment |
| Restriction: | Authority required (STREAMLINED) |
| Clinical criteria: | Patient must have previously been issued with an authority prescription for this drug |
| Administrative Advice | <u>NOTE:</u> Continuing Therapy Only 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

Eisai is pleased with the PBACs' decision to recommend approval of Fycompa for the defined patients with epilepsy. Eisai looks forward to working with the Health Minister and relevant departments to agree and finalise the conditions which enable a timely listing.