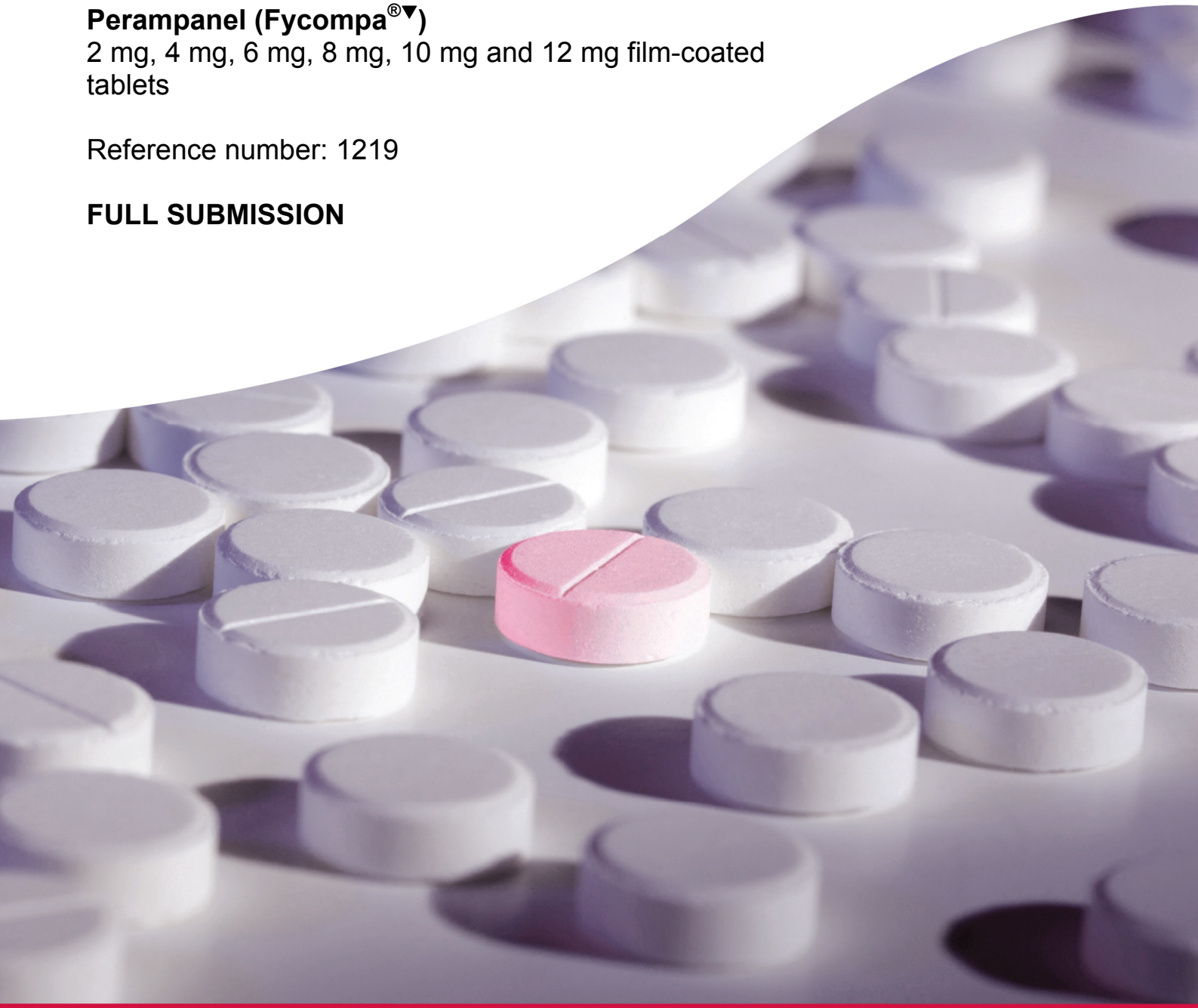
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Perampanel (Fycompa®▼)
2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg film-coated tablets

Reference number: 1219

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Perampanel (Fycompa®▼)
2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg film-coated tablets

This assessment report is based on evidence submitted by Eisai Ltd on 3 September 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Perampanel (Fycompa®▼) is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older[2].
Dosing	Perampanel should be initiated at a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Dose titration should be carried out once weekly or every two weeks, dependant on concomitant therapy. Perampanel should be taken orally once daily before bedtime. See Summary of Product Characteristics (SPCs) for further details[2].
Marketing authorisation date	23 July 2012[2]

2.0 DECISION CONTEXT

2.1 Background

Epilepsy is a common chronic neurological disorder characterised by recurrent seizures and affects approximately 23,000 people in Wales with approximately 1,500 developing epilepsy annually[3]. Epileptic seizures can be broadly categorised as either; partial-onset seizures, which originate in and affect only a localised part of the brain or generalised seizures, which are more widely distributed and affect both sides of the brain simultaneously. Seizures that spread from one side of the brain to the other are known as secondarily generalised seizures[4].

Two-thirds of patients with active epilepsy have their condition controlled by anti-epileptic drugs (AEDs). Where monotherapy with an AED is unsuccessful, adjunctive therapy is often considered[5]. If standard adjunctive therapy is ineffective or not tolerated, advice from a tertiary epilepsy specialist should be sought. National Institute for Health and Care Excellence (NICE) guidelines states that at this point the specialist may consider eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide or retigabine as a secondary adjunctive treatment[6].

Perampanel is a first-in-class selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist which reduces excitatory activity and excitotoxicity leading to anticonvulsant and antiepileptogenic effects[1]. The company has suggested that perampanel will be used for those patients whose seizures are still uncontrolled with first adjunctive therapy for partial-onset seizures. The company estimates that there are 4,446 patients in Wales with partial-

onset epilepsy who are refractory to therapy and therefore eligible for treatment with perampanel[1].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Lacosamide (Vimpat®)
- Retigabine (Trobalt®▼)
- Zonisamide (Zonegran®)

2.3 Guidance and related advice

- NICE. Clinical Guideline 137. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (2012)[5].
- NICE. Evidence summary. ESNM7: Partial-onset seizures in epilepsy: perampanel as adjunctive treatment. (2012)[6].
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults (2003)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of eslicarbazepine acetate in adult patients with epilepsy:

- Eslicarbazepine acetate (Zebinix®▼) is recommended as an option for restricted use within NHS Wales. Eslicarbazepine acetate (Zebinix®▼) should be restricted to treatment of highly refractory patients who remain uncontrolled with, or are intolerant to, other anti-epileptic medicine combinations, within its licensed indication as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation. Eslicarbazepine acetate (Zebinix®▼) is not recommended for use within NHS Wales outside of this subpopulation[8].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of three phase III trials[9–11], together with preliminary results from an open label extension (OLE) trial[12], comparing perampanel with placebo for the treatment of partial-onset seizures, with or without secondary generalisation. In addition the company has conducted a network meta-analysis (NMA) providing an indirect comparison between perampanel, lacosamide, retigabine and eslicarbazepine acetate[1].

3.1 Clinical effectiveness of perampanel versus placebo

The phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies 304, 305 and 306 compared perampanel with placebo in patients aged ≥ 12 years with partial-onset seizures with or without secondarily generalised seizures[9–11]. Patients were required to have uncontrolled seizures despite having been treated with at least two different AEDs, and receiving background therapy with one to a maximum of three concomitant AEDs. Since inducer AEDs, such as carbamazepine, phenobarbital, primidone and phenytoin are known to induce an enzyme involved in the metabolism of perampanel, only one concomitant inducer AED was permitted[1,13].

Each of the trials had three phases: a pre-randomisation phase, consisting of a screening visit and a six-week prospective baseline period; a double-blind phase, comprising a six-week titration period and a 13-week maintenance period and a follow-up phase of four weeks for patients who withdrew or did not enter the OLE study. During the six-week pre-randomisation phase, patients were required to have at least five partial seizures with two or more per three-week period and no seizure-free period > 25 days. At the end of the pre-randomisation period for trials 304 and 305, patients were randomly assigned to receive either placebo, 8 mg perampanel daily or 12 mg

perampanel daily. Trial 306 patients were randomly assigned to either placebo or perampanel at one of three daily doses: 2 mg, 4 mg or 8 mg. During the titration period doses were increased in 2 mg/week increments up to the target dose[1,13].

The primary endpoint for the intention to treat (ITT) population was the 50% responder rate, defined as the proportion of patients who experienced a 50% or greater reduction in the seizure frequency per 28 days of treatment. The responder rate was analysed for the maintenance period (with last observation carried forward), relative to the baseline from the pre-randomisation period. Secondary endpoints were the percentage change in the seizure frequency per 28 days during treatment, relative to baseline and the percentage change in the frequency of complex partial plus secondarily generalised seizures.

Studies 306 and 305 showed a statistically significant increase in the number of responders versus placebo for the 4 mg and 8 mg, and the 8 mg and 12 mg daily doses of perampanel, respectively. Study 304, however, did not show a statistically significant improvement in responder rates versus placebo for the 8 mg or 12 mg doses, neither was there a statistical difference for the 2 mg dose utilised in study 306. Statistical significant improvements were seen for the secondary endpoints in all three trials for doses greater than 2 mg (see Table 1 for detailed results).

Table 1. Primary and secondary efficacy results for perampanel

Primary and secondary efficacy results for perampanel (Study 306)					
	Placebo	**Perampanel 2 mg/day**	**Perampanel 4 mg/ day**	**Perampanel 8 mg/day**	**Perampanel 12 mg/day**
Primary endpoint – Responder rate†					
N	184	180	172	169	-
Number of responders (%)	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)	-
p value (vs placebo)	-	0.4863	0.0132	0.0003	-
Secondary endpoint – % change in partial seizure frequency per 28 days					
N	184	180	172	169	-
Median change	-10.69	-13.63	-23.33	-30.80	-
Median difference from placebo (95% CI)	-	-4.4 (-14.1–5.2)	-13.7 (-23.3–4.5)	-20.1 (-29.7–10.4)	-
p value (vs placebo)	-	0.4197	0.0026	<0.0001	-
Secondary endpoint – % change in complex partial plus secondarily generalised seizures per 28 days					
N	169	167	157	154	-
Median change	-17.63	-20.50	-31.18	-38.69	-
Median difference from placebo (95% CI)	-	-3.26 (-13.69–7.40)	-14.40 (-25.08–3.50)	-19.32 (-29.79– -8.63)	-
p value (vs placebo)	-	0.6506	0.0070	0.0005	-

Primary and secondary efficacy results for perampanel (Study 304)					
	Placebo	**Perampanel 2 mg/day**	**Perampanel 4 mg/ day**	**Perampanel 8 mg/day**	**Perampanel 12 mg/day**
Primary endpoint – Responder rate†					
N	121	-	-	133	133
Number of responders (%)	32 (26.4)	-	-	50 (37.6)	48 (36.1)
p value (vs placebo)	-	-	-	0.0760	0.0914
Secondary endpoint – Percentage change in partial seizure frequency per 28 days					
N	121	-	-	133	133
Median change	-20.95	-	-	-26.34	-34.39
Median difference from placebo (95% CI)	-	-	-	-13.53 (-26.17– -1.94)	-14.20 (-25.03– -2.73)
p value (vs placebo)	-	-	-	0.0261	0.0158
Secondary endpoint – % change in complex partial plus secondarily generalised seizures per 28 days					
N	110	-	-	120	120
Median change	-17.88	-	-	-33.03	-33.06
Median difference from placebo (95% CI)	-	-	-	-20.37 (-33.16– -7.74)	-17.90 (-30.31– -4.67)
p value (vs placebo)	-	-	-	0.0020	0.0081

Primary and secondary efficacy results for perampanel (Study 305)					
	Placebo	**Perampanel 2 mg/day**	**Perampanel 4 mg/ day**	**Perampanel 8 mg/day**	**Perampanel 12 mg/day**
Primary endpoint – Responder rate†					
N	136	-	-	129	121
Number of responders (%)	20 (14.7)	-	-	43 (33.3)	41 (33.9)
p value (vs placebo)	-	-	-	0.0018	0.0006
Secondary endpoint – Percentage change in partial seizure frequency per 28 days					
N	136	-	-	129	121
Median change	-9.72	-	-	-30.52	-17.57
Median difference from placebo (95% CI)	-	-	-	-19.10 (-29.17– -8.45)	-13.69 (-25.20– -2.26)
p value (vs placebo)	-	-	-	0.0008	0.0105
Secondary endpoint – % change in complex partial plus secondarily generalised seizures per 28 days					
N	126	-	-	119	113
Median change	-8.05	-	-	-32.72	-21.89
Median difference from placebo (95% CI)	-	-	-	-23.07 (-34.80– -10.55)	-17.45 (-29.27– -5.70)
p value (vs placebo)	-	-	-	0.0007	0.0045

†Patients who experienced ≥ 50% reduction in seizure frequency per 28 days versus baseline, CI: confidence interval
All endpoints are relative to baseline seizure frequency measured in the pre-randomisation period.

At the end of the phase III studies (304, 305 and 306) patients were able to enter a long term, ongoing OLE, study 307. The duration of study 307 was intended to be either approximately five years or until the product became commercially available. A total of 1,218 subjects entered the OLE study and the majority (n=1,084 [91%]) of patients were titrated to either 10 mg or 12 mg perampanel daily. Interim results showed that the responder rate for perampanel treated patients was maintained over a median duration of exposure of 51.4 weeks [12,13].

3.2 Indirect analysis of comparative efficacy

In the absence of studies providing a direct comparison between perampanel and the requested comparator treatments the submission includes an indirect comparison. The company carried out a systematic literature review to identify trials of adjunctive epilepsy therapies. A network meta-analysis (NMA) was carried out using 12 randomised placebo controlled trials (RCTs) of perampanel[9–11], lacosamide[14–16], eslicarbazepine acetate[17–19] and retigabine[20–22] for the endpoints: ≥ 50% reduction in seizure frequency (responder rate), seizure freedom and withdrawal due to adverse events. The odds ratios relative to placebo for the 50% responder rate (see Table 2) show that all AEDs performed significantly better than placebo. The credible intervals for the treatments overlap suggesting no significant differences between AEDs, although it should be noted that credible intervals are wide. When the different active comparators were evaluated for seizure freedom and withdrawal due to adverse events, none of the comparisons were significantly different.

Table 2: Odds ratio relative to placebo for the 50% responder rate[1].

	Placebo	Eslicarbazepine	Lacosamide	Retigabine
Eslicarbazepine acetate	2.753 (1.656–4.633)	-	-	-
Lacosamide	2.126 (1.332–3.495)	0.7732 (0.386–1.568)	-	-
Retigabine	2.857 (1.774–4.58)	1.037 (0.513–2.077)	1.346 (0.672–2.611)	-
Perampanel	2.151 (1.348–3.472)	0.7817 (0.392–1.579)	1.013 (0.513–1.963)	0.752 (0.389–1.491)
The numbers shown are the median odds ratios and credible intervals from the network meta analysis between the row defining treatment and the column defining treatment. Odds ratios greater than 1 favour the row defining treatment.				

3.3 Comparative safety

The most common treatment emergent adverse events (TEAEs) due to perampanel treatment were dizziness and somnolence[2,13]. Across the three phase III trials, dizziness was reported for 28% of patients receiving perampanel versus 9% of patients in the placebo arm and somnolence occurred for 15% of patients in the perampanel arm and for 7% of placebo-treated patients[13]. Fall was reported as a TEAE for perampanel and the risk of falling, especially in the elderly is noted in the SPC[2]. Psychiatric disorders such as insomnia, anxiety and aggression were reported by 15% of patients exposed to perampanel in the phase III studies[13]. The proportion of serious adverse events was higher with perampanel 12 mg daily (8.2%) and perampanel 8 mg daily (5.6%) compared with placebo (5.0%)[13].

The rate of discontinuation due to TEAEs was higher with perampanel 12 mg daily (19.2%) compared with the 8 mg/daily dose (7.7%) and placebo (4.5%) with the most common cause for discontinuation being dizziness[13]. Discontinuation rates for comparator treatments were: 8.1%–28.6% for lacosamide[23], 8.7%–19.3% for eslicarbazepine acetate[24] and 17.4–31.3% for retigabine[25]. No data directly comparing the safety profile for perampanel with any active comparator was included in the company submission.

3.4 AWTTC critique

- The licensed indication for perampanel is as adjunctive treatment for partial-onset epilepsy with or without secondarily generalised seizures. However the company has highlighted use in a narrower patient population; as a secondary adjunctive treatment, where the initial adjunctive treatment is unsuccessful or not tolerated[1,2]. This approach is supported by clinical expert opinion[6].
- AWTTC requested comparison of perampanel with lacosamide, retigabine and zonisamide. The company did not submit data for zonisamide as they considered that it was not an appropriate comparator because it can be used as monotherapy; eslicarbazepine acetate was provided as an alternative[1].
- Results of indirect comparisons should be interpreted with caution due to the inherent limitations in the method and the differences in the patient population across studies. It should, however, be noted that analysis conducted by the company showed that the effects of heterogeneity in the NMA were minimal.
- Results of the phase III studies showed that at daily doses of 4–12 mg perampanel was superior to placebo in efficacy. Although study 304 did not show statistical superiority in responder rate for perampanel compared to placebo this was driven by the high placebo response for the Central and South American regional subgroup. The Committee for Medicinal Products for Human Use (CHMP) concluded that it was reasonable to conclude that efficacy had been demonstrated and that the lack of significance in study 304 was not a concern[13].
- CHMP found no increase in efficacy between the 8 mg and 12 mg perampanel doses and the higher dose is associated with an increased number of adverse events (AEs). However, CHMP concluded that the 12 mg dose is beneficial in the patient sub-group who tolerate the 8 mg dose but obtain an insufficient clinical response[13].
- There is a lack of long term safety and efficacy data for perampanel and limited data in patients ≥ 65 years.
- Perampanel is licensed for patients aged ≥ 12 years[2], whilst lacosamide is recommended in patients ≥ 16 years[26] and eslicarbazepine acetate[27] and retigabine[28] are licensed in patients ≥ 18 years.
- Perampanel[2] and eslicarbazepine acetate[27] are available as once daily treatments, whilst lacosamide[26] and retigabine[28] tablets are taken twice and three times daily respectively.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis (CUA) and cost minimisation analysis (CMA) of the use of perampanel as a second-line adjunctive treatment for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older[1]. As the licensed indication for perampanel does not limit its use to second-line, the economic evidence provided by the company is restricted to a subset of the wider licensed indication[2].

Perampanel has been compared against lacosamide, retigabine and eslicarbazepine acetate using a Markov model with a six-month cycle length and two-year time horizon of analysis in the base case. The company suggests lacosamide is the most relevant comparator, based on prescription volume analysis that suggests it is the most frequently used of these adjunctive AEDs. AWTTC also requested comparison against zonisamide, but the company has suggested this medicine would be used earlier as monotherapy, and so has not been considered as a comparator in its analyses. In the absence of direct comparative data, the company has conducted adjusted indirect treatment comparisons using placebo-controlled trials of perampanel and the

comparators, to determine the probabilities of response to treatment (defined as patients achieving ≥50% reduction in seizure frequency), complete seizure freedom and withdrawals due to adverse events for use in the model. The company has suggested these are comparable for perampanel and the comparator AEDs. However, for the CUA, these probabilities are applied for the first six-month cycle, with response to treatment in subsequent cycles assumed independent of treatment received and based on probabilities obtained from a published study of the cost-effectiveness of other AEDs[29]. The probabilities of complete seizure freedom derived from the indirect treatment comparison are applied in the first cycle, and are assumed to remain constant in all subsequent cycles. Withdrawal due to adverse events is assumed to occur only in the first cycle, and other adverse events are not considered[1].

Utility values applied to health states are treatment-independent, and are based on a published study, with alternative values explored in sensitivity analyses[30]. Medication acquisition costs are based simply on the mean of the minimum and maximum recommended doses for each AED. Perampanel acquisition costs are based on the confidential price agreed in a Welsh Patient Access Scheme (WPAS). Non-drug resource use includes GP and outpatient visits associated with treatment changes and follow up, and other resource use associated with seizures, the probabilities of which are based on a published UK study from 1998[31]. Costs and outcomes beyond one year were discounted at 3.5% per annum.

4.1.2 Results of the company analyses

The results of the company's base case CUA are presented in Table 3. The company concludes that the additional cost of perampanel compared with lacosamide (its most relevant comparator) is negligible, and compared with retigabine is minimal; perampanel is cost saving compared with eslicarbazepine acetate. There was no difference in quality-adjusted life-years (QALYs) for perampanel and lacosamide, but versus retigabine and eslicarbazepine acetate, perampanel was modelled to be less effective by 0.01 QALYs over two years.

Table 3: Estimated costs and QALYs over 2-year time horizon in the company's base case cost-utility analyses.

Treatment	Treatment costs	Other costs	Total costs	QALYs	Incremental costs (Perampanel vs. Comparator)	Incremental QALYs (Perampanel vs. Comparator)	Notes
Perampanel	£1,961	£1,432	£3,393	1.664	-	-	
Lacosamide	£1,953	£1,430	£3,383	1.664	£9	0	Perampanel same effectiveness and more costly
Retigabine	£1,898	£1,441	£3,339	1.674	£53	-0.01	Perampanel less effective and more costly
Eslicarbazepine acetate	£2,445	£1,423	£3,867	1.673	-£475	-0.011	Perampanel less effective and less costly (ICER: £43,182 saved per QALY foregone)
Standard care	£486	£1,438	£1,924	1.645	£1,469	0.02	Perampanel more effective and more costly (ICER: £73,450 per QALY gained)

In one way sensitivity analyses exploring: an alternative way of estimating the dose and costs of comparators, a 15-year time horizon of analysis, the range of the credible intervals around efficacy estimates, an alternative source of utility values, and discount rates, the model outputs were largely unchanged from the results of the base case CUA. As perampanel has the same cost irrespective of tablet strength, when the maximum doses of AEDs were considered, perampanel was cost saving compared with all comparators (savings of £339 to £776); however, not all patients will require the maximum doses of AEDs and the base case analysis reflects the most plausible dosing assumptions.

A scenario analysis of use in the subgroup of patients with partial onset seizures with secondary generalisation indicates perampanel to be cost saving by £18 compared with lacosamide. In the subgroup of patients with complex partial seizures perampanel is more costly than lacosamide by £12. Data for other comparators in these subgroups are not available.

The company suggests that the indirect treatment comparison demonstrates similar efficacy for perampanel and the comparators, and therefore a cost minimisation analysis would be appropriate. Incremental costs of perampanel versus the comparators are presented in Table 4.

Table 4: Estimated incremental costs of perampanel versus comparators over a 2-year time horizon in the company's cost minimisation analyses

	Perampanel - Lacosamide	Perampanel - Retigabine	Perampanel - Eslicarbazepine acetate	Perampanel – Standard care
Base case	+£3	+£146	-£356	+£1,469
Scenarios				
Maximum drug doses only	-£472	-£339	-£751	+£1,468
Partial onset seizures with secondary generalisation	+£52 (mean doses) £0 (cost/tablet basis)	n/a	n/a	+£1,540 (mean doses) +£1,695 (cost/tablet basis)
Complex partial seizures	+£49 (mean doses) £0 (cost/tablet basis)	n/a	n/a	+£1,441 (mean doses) +£1,581 (cost/tablet basis)

4.1.3 AWTTC critique

The reliability of the company's cost minimisation analysis is dependent on the extent to which perampanel has been demonstrated to be therapeutically equivalent to the comparators. There is a lack of direct comparative data for perampanel and the AED comparators currently in use in Wales. The indirect treatment comparison reports no statistically significant differences between perampanel and the AED comparators for important endpoints of ≥50% reduction in seizure frequency, seizure freedom and withdrawals from treatment due to adverse events based on the overlap of all credible intervals around point estimates; however, the credible intervals are very wide, reflecting uncertainty and a lack of precision in the relative estimates, and there are numerical differences in favour of the comparators for reductions in seizure frequency and seizure freedom. In both the cost minimisation analysis and the cost utility analysis (based on the WPAS-agreed price), perampanel appears to be associated with similar costs to lacosamide (the most relevant comparator), additional costs

compared with retigabine and with cost savings compared with eslicarbazepine acetate. In the cost utility analysis, perampanel is more costly and less effective than retigabine, and is both less costly and less effective than eslicarbazepine acetate.

Strengths of the economic evidence:

- In the absence of direct comparative data, the company has conducted a systematic literature review to identify studies of comparators for inclusion in adjusted indirect treatment comparisons.
- The indirect treatment comparison considers multiple relevant endpoints.

Limitations of the economic evidence:

- There is a lack of direct comparative data for perampanel against relevant comparators. The trials included in the indirect treatment comparisons differed with respect to the number of prior and concomitant AEDs, although sensitivity analysis conducted by the company showed that the effects of heterogeneity were minimal. However, none of the trials specifically tested the AEDs as second-line adjunctive agents.
- Based on the overlap of all credible intervals around point estimates derived from the indirect treatment comparisons, the company concludes there are no statistically significant differences in outcomes for patients receiving perampanel and any other comparator; however, the credible intervals for each outcome measure are wide, indicating a lack of precision and uncertainty. The numerical differences translate into absolute differences in probabilities for response (≥50% reduction in seizure frequency) in the first Markov cycle of up to 10% (perampanel 41.7% versus eslicarbazepine acetate 51.8%).
- For the subgroup analyses, whilst response to perampanel was statistically significantly improved compared with placebo in those with partial onset seizures and secondary generalisation at baseline, there was no statistically significant difference observed for lacosamide, and neither agent provided statistically significant improvement in response compared to placebo in the subgroup with complex partial seizures at baseline.
- Probabilistic sensitivity analyses, which take account of the combined uncertainty in parameter estimates, confirm the small differences that exist in effectiveness (QALY) estimates between perampanel and the comparators. The resultant cost-effectiveness acceptability curves suggest that, relative to standard of care (placebo arm of the trials included in the indirect treatment comparison), none of the adjunctive AEDs considered in this analysis have a high probability of being cost-effective at the usual threshold range of £20,000 to £30,000 per QALY gained. Perampanel appears to have the lowest probability of being cost-effective, reflecting its numerically lower probabilities of achieving a ≥ 50% reduction in seizures and seizure freedom compared with the comparator AEDs.
- Collectively, there is uncertainty in the relative effectiveness estimates, and the small modelled differences make interpretation of the modelled outputs difficult.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of perampanel within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Welsh statistics, the company estimates there to be 22,548 patients with epilepsy in Wales, and 1,203 incident cases each year. Around 52% of these are estimated to have partial or secondarily generalised seizures, based on a UK general practice study published in 1990[32], of which 36% are estimated to have refractory epilepsy based on a study in one tertiary centre in Scotland, 2000[33]. Therefore, the company estimates there to be 4,446 patients potentially eligible for treatment with perampanel; however, based on company market uptake projections, 0.4% are anticipated to receive perampanel in year one, rising to 10.4% in year five. It is assumed that perampanel will displace only lacosamide.

Costs such as those arising from one-year drug acquisition, follow-on therapy, GP and outpatient visits, and accident and emergency attendance are derived from the economic model. Results of the budget impact analysis are presented in Table 5. Given that the estimates of net budget impact are small, the company has not conducted any further sensitivity/scenario analyses.

5.1.2 Results

Table 5: Company estimates of net budget impact of perampanel

	Year 1	**Year 2**	**Year 3**	Year **4**	**Year 5**
Number of eligible patients (indication(s) covered in this submission)	4,446	4,671	4,896	5,121	5,347
Uptake (%)	0.4%	3.2%	6.5%	8.5%	10.4%
Perampanel treated patients	16	149	320	434	557
Total costs all eligible patients *without* perampanel uptake	£10,408,861	£10,935,892	£11,462,923	£11,989,954	£12,516,985
Total costs all eligible patients *with* perampanel uptake	£10,408,922	£10,936,467	£11,464,155	£11,991,627	£12,519,132
Net costs (incremental)					
Drug costs	£43	£408	£875	£1,188	£1,525
Administration and monitoring	£0	£0	£0	£0	£0
Primary care	£0.0	-£0.1	-£0.2	-£0.3	-£0.4
Secondary & tertiary care	£18	£167	£358	£485	£623
Overall net cost (incremental)	£61	£575	£1,232	£1,673	£2,148

5.1.3 AWTTC critique

- The sources used to estimate eligible patient numbers appear dated, given the range of newer AEDs that have become available over the last 15-20 years since these sources were published. It is unclear if the proportion estimated to be refractory to AED treatment (36%) reflects the patients who require a second-line adjunctive AED, which is the place in therapy that the company has requested AWMSG to consider the use of perampanel. Therefore, the number of patients likely to receive perampanel in practice appears uncertain.
- The cost estimates are derived from the economic model, and therefore the uncertainties in the economic model in relation to comparative effectiveness, which impact on follow on treatments and resource use, are also applicable to the budget impact analyses.
- Collectively, there are a range of uncertainties in the budget impact analysis, but under the WPAS agreed price for perampanel, its acquisition costs are practically the same as for lacosamide at mean doses.

5.2 Table of comparative unit costs

Most AEDs can be used as adjunctive therapy in the treatment of partial onset seizures. Table 6 includes example drug acquisition costs for selected newer AEDs that may be used as adjuvant agents, based on their current list prices. Perampanel has an approved WPAS which includes a confidential discount on the list price.

Table 6: Examples of acquisition costs of antiepileptic agents used as adjunctive treatment for partial onset epilepsy.

Treatment	Example dose†	Cost per year
Perampanel (Fycompa®▼) tablets	4 mg to 12 mg once daily	£1,825 (based on full list price)
Eslicarbazepine (Zebinix®) tablets	800 mg to 1,200 mg once daily	£1,679 to £2,519
Lacosamide (Vimpat®) tablets	50 mg to 200 mg twice daily	£564 to £1,879
Retigabine (Trobalt®▼) tablets	100 mg to 400 mg three times daily	£507 to £1,664
Zonisamide (Zonegran®) capsules	25 mg twice daily to 500 mg in one or two divided doses	£460 to £2,044

Costs based on MIMS list prices as of 14 January 2013[34].
†Based on MIMS stated usual doses[34].
This table does not imply therapeutic equivalence of the stated drugs and doses.
Note perampanel is licensed for use in children aged 12 years and older. Other agents are licensed for use in patients of different ages. See all relevant SPCs for full dosing details[2,26–28,35].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, Perampanel (Fycompa®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

6.2 Ongoing studies

The company anticipates that further results will be available from the OLE, study 307 before May 2013. Additionally, study 235, an ongoing, randomised, double-blind, placebo-controlled trial of adjunctive treatment with perampanel on cognition, growth, safety, tolerability and pharmokinetics in adolescents (aged 12 to < 18 years) will reach its estimated primary completion date in March 2013[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 10 December 2012
Date range of evidence search: No date limits were applied to database searches

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