

perampanel, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg film-coated tablets
(Fycompa®) SMC No. (819/12)

Eisai Ltd

09 November 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

perampanel (Fycompa®) is accepted for restricted use within NHS Scotland.

Indication under review: Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

SMC restriction: use as a second-line adjunctive treatment in patients with refractory partial onset epilepsy. Treatment should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

In three placebo-controlled studies in patients with uncontrolled partial-onset seizures, perampanel was superior to placebo in terms of the proportion of patients experiencing a $\geq 50\%$ reduction in partial seizure frequency per 28 days.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of perampanel. This SMC advice is contingent upon the continuing availability of the patient access scheme or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.

Dosing Information

Perampanel must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability. Perampanel should be taken orally once daily before bedtime.

Treatment with perampanel should be initiated with a dose of 2mg/day. The dose may be increased based on clinical response and tolerability by increments of 2mg/day to a maintenance dose of 4mg/day to 8mg/day. Depending upon individual clinical response and tolerability at a dose of 8mg/day, the dose may be increased by increments of 2mg/day to 12mg/day.

Product availability date

September 2012

Summary of evidence on comparative efficacy

Perampanel is an antiepileptic drug (AED) with a novel mechanism of action. It is a selective non-competitive antagonist of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS).¹

Perampanel is licensed for the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers perampanel when positioned for use as a second-line adjunctive treatment in patients with refractory partial onset epilepsy i.e. patients who have previously received monotherapy and are not seizure free after at least one other adjunctive therapy.

Three phase III randomised, double-blind, placebo-controlled, parallel-group studies of similar design were conducted in patients aged ≥ 12 years with a diagnosis of epilepsy with partial seizures, with or without secondary generalisation. The studies recruited patients who had uncontrolled seizures despite having been treated with at least two different AEDs within approximately the last two years. Patients must have had five or more partial onset seizures during a 6-week baseline period, which included at least two partial onset seizures during each 3-week period and no seizure-free period of longer than 25 days. All patients were receiving at least one and up to a maximum of three concurrent AEDs, which had been used at a stable dose for at least 49 days before the first study visit. In two of the studies patients were randomised equally to perampanel 8mg daily, perampanel 12mg daily or placebo and in the third study patients were randomised equally to perampanel 2mg daily, perampanel 4mg daily, perampanel 8mg daily or placebo. In all three studies, perampanel was initiated at a dose of 2mg and was increased in increments of 2mg/day each week until the target dose was achieved. The titration period was 6 weeks in all studies, irrespective of whether the target dose

was achieved before this. After titration, patients entered a 13-week maintenance period, after which time they could either enter an open-label extension study or stop study treatment. Patients who stopped study treatment were followed up after 4 weeks. Approximately 400 patients were randomised in each of the two higher dose studies, and approximately 700 patients were included in the lower dose study. Patients (or their caregiver) recorded all simple partial seizures, complex partial seizures and complex partial seizures with secondary generalisation in a daily seizure diary.^{2,3}

The primary endpoint was the 50% responder rate, which was defined as the proportion of patients who experienced a 50% or greater reduction in partial seizure frequency per 28 days in the study maintenance period compared with the pre-randomisation period. The primary efficacy outcome was analysed in the intent-to-treat (ITT) population using the Cochran-Mantel-Haenzel test. A key secondary outcome was the percentage change in partial seizure frequency per 28 days during the double-blind phase from the pre-randomisation phase, analysed in the ITT population. The results of the primary outcome and the key secondary outcome in each of the three studies are shown in the table below.^{2,3}

Table 1. Results for the primary endpoint of 50% responder rate and the key secondary outcome of in each of the three studies.^{2,3}

Treatment allocation	n (full ITT population)	Proportion of responders	Percentage change in partial seizure frequency
Study 1			
Perampanel 8mg	133	38% (50/133)	-26%*
Perampanel 12mg	133	36% (48/133)	-34%*
Placebo	121	26% (32/121)	-21%
Study 2			
Perampanel 8mg	129	33% (43/129)*	-31%*
Perampanel 12mg	121	34% (41/121)*	-18%*
Placebo	136	15% (20/136)	-9.7%
Study 3			
Perampanel 2mg	180	21% (37/180)	-14%
Perampanel 4mg	172	28% (49/172)*	-23%*
Perampanel 8mg	169	35% (59/169)*	-31%*
Placebo	184	18% (33/184)	-11%

*statistically significant compared with placebo; p<0.05

There was a statistically significant improvement in the proportion of responders for perampanel 4mg (study 3), perampanel 8mg (studies 2 and 3) and perampanel 12mg (study 2). There was a statistically significant difference in favour of perampanel for the percentage change in partial seizure frequency for perampanel 4mg (study 3), perampanel 8mg (studies 1 to 3) and perampanel 12mg (studies 1 and 2).

Other secondary outcomes, analysed in the ITT population, included; the percentage change from baseline in the frequency of complex partial plus secondary generalised seizures; percentage of patients who achieved seizure-free status; and Clinical and Patient Global Impression of Change.

The results for the percentage change in frequency of complex partial plus secondary generalised seizures were consistent with those for the key secondary outcome of percentage

change in partial seizure frequency. There was no statistically significant difference between treatment groups in the percentage of patients who achieved seizure-free status in any of the studies. Quality of life was assessed in all three studies using the Quality of Life in Epilepsy (QOLIE-31-P) subscale, and it was similar in all groups.^{2,3}

Approximately 1200 patients were enrolled into the 5-year open-label extension study up to the time of the data cut-off for the interim analysis, which included equal numbers from each of the three phase III studies. 10% of patients were adolescents. The co-primary outcomes for the open-label extension study were percentage change in partial seizure frequency per 28 days, relative to pre-perampanel baseline and the 50% responder rate as described above. The results of the interim analysis, which included data up to 2 years showed that efficacy of perampanel was maintained over time, although the number of patients analysed for longer treatment durations was low.

Summary of evidence on comparative safety

No comparative safety data are available.

The most commonly reported adverse events in the phase III studies concerned the central nervous system (CNS). Dizziness and somnolence were the most frequently reported adverse events (>10%)¹; other commonly reported adverse events included ataxia, balance disorder, dysarthria and irritability. Psychiatric disorders including anger, aggression, anxiety and confusion were also commonly reported.^{1,2}

Adverse events leading to treatment discontinuation were reported in 1.7%, 4.2% and 14% of patients in the perampanel 4mg, 8mg and 12mg groups respectively, compared with 1.4% of patients who received placebo. The most common adverse events leading to discontinuation were dizziness and somnolence.¹ A dose-related increase in frequency was noted for a number of the most common adverse events that led to treatment discontinuation (i.e. dizziness, ataxia, aggression, anxiety, vertigo, irritability and fall).²

Balance disorders, falls (particularly in the elderly), and aggression were identified as potential safety concerns during the regulatory approval process.²

Summary of clinical effectiveness issues

Current treatment guidelines recommend that in patients with refractory focal seizures, adjunctive treatment may be offered with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate. If this adjunctive treatment is unsuccessful, then a tertiary epilepsy specialist may consider treatment with another AED including eslicarbazepine, lacosamide, pregabalin, tiagabine, vigabatrin or zonisamide. The submitting company has requested that SMC considers the use of perampanel when positioned for use as a second-line adjunctive therapy in patients with refractory partial onset epilepsy i.e. those who have received treatment with monotherapy and at least one other adjunctive therapy. SMC clinical experts have confirmed that the company's proposed positioning is reasonable.

Three similarly designed randomised, placebo-controlled clinical studies were presented, two examining the higher doses of perampanel of 8mg and 12mg and one studying lower doses of

2mg, 4mg and 8mg perampanel. The three studies showed a consistent treatment effect for the main primary and secondary outcomes, however, there were some limitations.

The study populations represent a wider patient population than those reflected in the submitting company's proposed positioning i.e. eligible for a second adjunctive therapy. Patients were required to be taking at least one and a maximum of three concurrent AEDs; in general the treatment groups were well-matched with respect to both the number and type (enzyme inducer or non-enzyme inducer) of concurrent AEDs. In all three studies, the majority of patients ($\geq 85\%$) were taking two or more concurrent AEDs. It is unclear whether this level of concurrent AED administration would reflect clinical practice in Scotland.

Patients in the studies underwent a forced titration of perampanel to the randomised treatment dose, with no allowance for subsequent dose adjustment over the course of the study. There was a slightly higher drop-out rate in the perampanel 12mg treatment group in both the higher dose studies, which was principally due to treatment discontinuations due to adverse events. This may introduce bias, by artificially increasing the response rate of perampanel 12mg.

There was an unusually high placebo response reported in one geographic region in one of the higher dose studies, which resulted in a non-statistically significant result for the primary outcome. Analysis of the study, excluding patients from this region, did result in a statistically significant result.²

The studies included a very low number of patients aged 64 years or over,² so it is uncertain whether the study results are generalisable to the elderly population in Scotland. Elderly patients may be more susceptible to the CNS adverse effects of perampanel and falls in the elderly have been identified as a potential safety concern.

The potential for abuse and dependence was identified as a possible safety concern during the regulatory approval process.² Tolerability may be a concern, due to the high incidence of dizziness.

Perampanel is licensed in adolescent patients aged ≥ 12 years. This offers an advantage over other recently licensed AEDs for adjunctive treatment of partial onset seizures, which are licensed in adults aged ≥ 16 years (e.g. lacosamide) or ≥ 18 years or over (e.g. eslicarbazepine acetate, retigabine).

Perampanel is administered once daily, compared with lacosamide (twice daily dosing) and retigabine (three times a day dosing).

No comparative data with other AEDs are available. To support the economic analysis, the company presented a Bayesian network meta-analysis in which perampanel was indirectly compared with lacosamide, retigabine and eslicarbazepine. The network of evidence comprised 12 randomised, placebo-controlled studies in patients aged ≥ 12 years with refractory partial (focal) onset epilepsy with or without secondary generalisation who received the AED as adjunctive treatment. Three outcomes were compared: the 50% responder rate, the proportion of patients with seizure freedom, and the proportion of patients withdrawing due to adverse events. The primary analysis was conducted using a random-effects model and no statistically significant difference between the treatments was found. Sources of clinical and methodological heterogeneity between the studies were tested in several sensitivity analyses and these did not significantly alter the results. In terms of the external validity of the network meta-analysis, patients recruited to the included studies comprised a wider patient population than the one

proposed to be treated by the submitting company i.e. eligible for second adjunctive therapy. There was not a specific inclusion criterion for patients to already be treated with adjunctive therapy. Inclusion was based on patients having seizures despite current treatment (between 1 and 3 AEDs). It is not known if the results can be extrapolated to this selected group.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis of perampanel as a second adjunctive AED in patients with refractory partial onset epilepsy i.e. patients who have been trialled on monotherapy and at least one further combination therapy. The comparators in the analysis were retigabine, lacosamide and eslicarbazepine acetate. A 2 year time horizon was used.

The clinical evidence to support the use of a cost-minimisation analysis came from the results of the network meta-analysis (NMA) that showed similar efficacy and safety between perampanel and the comparator AEDs.

The analysis compared the total costs per patient for perampanel versus the comparator AEDs. Costs included drug costs, inpatient visits, A&E services, outpatient and GP visits.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. The PAS offered a simple discount on the list price of perampanel. With the PAS, the results showed that the total cost per patient (over the 2 year time horizon) for perampanel was £3,479 compared to retigabine at £3,334 indicating perampanel would be associated with an incremental cost of £145 and therefore would not be the preferred treatment on cost-minimisation grounds. When compared to lacosamide, perampanel is cost neutral when the PAS is applied. The results also showed that the total cost per patient (over the 2 year time horizon) for eslicarbazepine acetate was £3,834 indicating perampanel would be associated with cost savings of -£355 under the conditions of the PAS and would therefore be the preferred treatment on cost minimisation grounds. The submitting company also provided an analysis assuming a weighted average comparator with the predominant treatment being lacosamide. Perampanel was the preferred treatment on cost-minimisation grounds in this scenario.

Subgroup analyses were also presented for patients with secondary generalised seizures at baseline (aged ≥ 12 years) and patients with complex seizures at baseline (aged ≥ 12 years). For the subgroup of patients with secondary generalised seizures at baseline, with the PAS the results showed the total cost per patient (over the 2 year time horizon) for perampanel was cost-neutral compared to lacosamide. For the subgroup of patients with complex seizures at baseline, with the PAS, perampanel was associated with an incremental cost of £1 compared to lacosamide.

The sensitivity analyses showed that perampanel is associated with an incremental cost when compared to retigabine and cost savings when compared to lacosamide and eslicarbazepine acetate, when all AEDs are used at the maximum dose.

The cost minimisation analysis results show that with the PAS, perampanel is cost-effective against some but not all comparators. However, given that lacosamide is likely to be the most widely prescribed of the AEDs, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

SIGN guideline 70. Diagnosis and Management of Epilepsy in Adults (2003) is currently being updated.

NICE published clinical guideline number 137 Epilepsy in January 2012. This recommends that adjunctive or 'add-on' therapy should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. The choice of AED should be based on the presenting epilepsy syndrome, or, if this is not clear at the time of presentation, on the presenting seizure type. The guidance recommends carbamazepine or lamotrigine as the first-line therapy for focal seizures; if the first AED tried is ineffective then an alternative may be tried from among these five AEDs: lamotrigine, carbamazepine, levetiracetam, oxcarbazepine or sodium valproate. In patients with refractory focal seizures, adjunctive treatment may be offered with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate. If adjunctive treatment is unsuccessful, then a tertiary epilepsy specialist may consider treatment with eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.

Additional information: comparators

The majority of AEDs can be used within their licensed indications as adjunctive treatment for partial seizures with or without secondary generalisation. In practice the older drugs (e.g. carbamazepine and sodium valproate) tend to be used as first-line treatments, with the newer AEDs used as adjunctive therapy in patients not controlled with monotherapy.

Comparators relevant to the licensed indication have been included in the table below.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
perampanel	4mg to 12mg orally once daily before bedtime	1,820*
eslicarbazepine acetate	800mg to 1,200mg orally once daily	1,650 to 2,475
zonisamide	25mg orally twice daily to 500mg orally daily in one or two divided doses.	459 to 2,038
lacosamide	50mg to 200mg orally twice daily	562 to 1,874
tiagabine	15mg to 45mg orally daily in two or three divided doses	568 to 1,705
retigabine	100mg to 400mg orally three times daily	506 to 1,660
pregabalin	150mg to 600mg orally daily in two or three divided doses	837 [#]
vigabatrin	1,000mg to 3,000mg orally daily in one or two divided doses	225 to 674
phenytoin	200mg to 500mg orally in single or divided doses.	25 to 61
phenobarbital	60mg to 180mg orally once daily before bedtime	9 to 27

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 September 2012.

*Cost taken from company submission and is the same for all tablet strengths.

[#] Cost based on two divided doses.

Additional information: budget impact

Without PAS:

The submitting company estimated the population eligible for treatment to be 10,450 in Year 1 rising to 12,385 in Year 5 with an estimated uptake rate of 0.36% in year 1 and 10.42% in year 5. The gross impact on the medicines budget was estimated to be £50k in year 1 and £1.730m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £3k in year 1 and £117k in year 5.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

- 1) Eisai Ltd. Summary of product characteristics - Fycompa 2mg, 4mg, 6mg, 8mg, 10mg, 12mg film-coated tablets. Available from www.medicines.org.uk [Last updated 30 August 2012]
- 2) European Medicines Agency. European Public Assessment Report – Fycompa. Procedure No: EMEA/H/C/002434. Available from www.ema.europa.eu [Last updated 07 August 2012]
- 3) Krauss GL, Serratos JM, Villanueva V et al. Randomized phase III study 306: Adjunctive perampanel for refractory partial-onset seizures. *Neurology* (2012); 78: 1408-15.

This assessment is based on data submitted by the applicant company up to and including 12 October 2012.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in

determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.