



**North East Treatment  
Advisory Group**

# **Perampanel for epilepsy**

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## Summary

- Perampanel is a first-in-class once-daily anti-epileptic drug licensed for adjunctive treatment of partial-onset seizures, with or without secondarily generalised seizures, in patients with epilepsy aged  $\geq 12$  years.
- Perampanel in epilepsy has been evaluated in three phase 3 placebo-controlled studies involving nearly 1,500 patients. These studies demonstrated modest but significant benefits for perampanel in a range of outcomes in treatment-refractory patients. In particular, perampanel was associated with marked reductions in seizure frequency in some patients. Limited longer-term evidence indicates that initial efficacy results are maintained.
- The safety of perampanel has been evaluated primarily in the phase 3 studies. Perampanel is associated with a substantial burden of adverse effects although the patient group was also using multiple concomitant medications. Most adverse effects were mild or moderate in severity.
- The most common adverse effects were dizziness, somnolence, headache and fatigue. The incidence of adverse events was high in all treatment groups including placebo. Events were predominantly mild or moderate in severity. Serious adverse events affected about 1 in 8 patients with follow-up of about one year.
- The treatment discontinuation rate due to adverse effects was about 10% during short-term observation, increasing to only 13% with longer-term follow-up of about one year.
- Perampanel is a relatively costly anti-epileptic drug at a fixed £1,825 per patient per annum regardless of dose. This is slightly more costly than estimated mean treatment costs for other newer anti-epileptic drugs which are recommended by NICE. However the actual cost of other anti-epileptic drugs is directly linked to the dose and could therefore exceed the cost of perampanel.
- Based on the current primary care use of other new anti-epileptic drugs, the budget impact of perampanel is crudely estimated at £155,000 per annum after four years, corresponding to 85 patients.

## Introduction and background

Epilepsy is a common neurological disorder characterised by recurrent seizures which are not provoked by an immediately identifiable cause. There are at least 40 different types of epileptic seizures which can be broadly categorised into two main classifications depending on the source of the seizure within the brain; partial, or focal, onset seizures originate in and affect only a part of the brain; generalised seizures are more widely distributed and affect both sides of the brain simultaneously. Seizures which spread from one side of the brain to the other are known as secondarily generalised seizures.<sup>1-4</sup>

Due to the complex nature of epilepsy accurate estimates of incidence and prevalence are difficult to establish. In 2011 the Joint Epilepsy Council (JEC) estimated there were approximately 600,000 adults in the UK with a diagnosis of epilepsy who were receiving anti-epileptic drugs (AED). The UK incidence is estimated to be around 50 cases per 100,000 of the population per year. Life expectancy is reduced by up to 10 years for people with symptomatic epilepsy, and there are around 1,000 epilepsy related deaths per year in the UK. Sudden unexpected death in epilepsy accounts for around half of all epilepsy deaths, of which around 40% are thought to be potentially avoidable.<sup>3-5</sup>

For many patients epileptic seizures can be controlled through treatment with an AED. Current NICE guidelines recommend carbamazepine or lamotrigine as first-line treatment for young people and adults with newly diagnosed focal seizures.<sup>6</sup> Levetiracetam, oxcarbazepine or sodium valproate are recommended if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, an alternative from these five AED should be offered. Adjunctive treatment should be considered if a second well-tolerated AED is ineffective. Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate are recommended as adjunctive treatments. Retigabine is recommended as an option only when these treatments fail to provide an adequate response or are not tolerated.<sup>6</sup> Approximately 60% of newly diagnosed patients will achieve sustained seizure freedom with monotherapy, and an additional 15-20% with polytherapy. However, 20-30% of patients do not achieve satisfactory seizure remission with any drug therapies.<sup>2-4,6-8</sup>

Perampanel (Fycompa®, Eisai) is an orally active, non-competitive glutamate receptor antagonist. It demonstrates novel pharmacology and is the first licensed drug which specifically and selectively inhibits the AMPA-type of glutamate receptor. Perampanel is licensed for adjunctive treatment of partial-onset seizures, with or without secondarily generalised seizures, in patients with epilepsy aged 12 years and older. Perampanel is administered orally, once-daily, typically at bedtime.<sup>9,10</sup>

NICE has issued guidance on the use of AED for the treatment of partial (focal) seizures.<sup>6</sup>

**Box 1.** NICE guidance on pharmacological treatment of focal (partial) seizures (abridged excerpt)<sup>6</sup>

Adjunctive treatment in children, young people and adults with refractory focal seizures:

Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to children, young people and adults with focal seizures if first-line treatments are ineffective or not tolerated.

If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.

Note that some of these treatments are not licensed for use in children, or are licensed only in children with a minimum age stipulated.

This guidance was issued in January 2012 before perampanel was available and therefore perampanel is not referred to in the guidance. Retigabine, (Trobal®) is a potassium channel activator also licensed for partial onset seizure epilepsy.<sup>1</sup> Retigabine is not referred to in the NICE clinical guideline for epilepsy,<sup>6</sup> possibly as the drug became available only after the guideline update had commenced. It was launched in May 2011 and recommended by NICE via a single technology appraisal in July 2011 for adult patients.<sup>1</sup>

This report will review the evidence for the efficacy, safety, cost and practical implications of using perampanel for the control of epilepsy within its licensed indication.

## Clinical evidence

### **Controlled phase 3 studies** <sup>8,11-13</sup>

Three phase 3 studies which evaluated the efficacy of perampanel as adjunctive therapy for the treatment of partial-onset seizures, with or without secondarily generalised seizures, have been published. The studies were similarly designed multicentre, randomised, double-blind, placebo-controlled, parallel group trials involving 1,480 patients. Study 306 identified the minimal effective dose and included four treatment arms (placebo vs. perampanel 2 mg, 4 mg and 8 mg).<sup>13</sup> Studies 304 and 305 evaluated an extended dose range and included three treatment arms (placebo vs. perampanel 8 mg and 12 mg).<sup>11,12</sup> Each study consisted of three distinct phases: a six-week pre-randomisation phase to determine eligibility, a 19-week double-blind phase which consisted of a six-week titration period and a 13-week fixed dose maintenance period, and a follow-up phase of four-weeks. During the titration phase treatment was initiated at 2 mg daily increased in weekly increments of 2 mg daily to the end dose. If intolerable adverse events were experienced then patients could remain on the same dose or the dose was reduced to the previously tolerated dose. Patients who completed the double-blind phase had the option to enter a long-term extension study (study 307) and receive treatment with open-label perampanel.<sup>14</sup>

Patients had a diagnosis of epilepsy with partial seizures. The majority of patients (71%) had secondarily generalised seizures. All patients had failed to respond adequately to at least two AEDs in the previous two years, and were taking stable doses of up to three approved AEDs.<sup>15</sup> Only one inducer-AED (i.e. carbamazepine, phenytoin, phenobarbital, or primidone) was permitted and concomitant benzodiazepine use had to be limited and stable in the month prior to randomisation. During the six-week pre-randomisation phase patients were required to have at least five partial seizures with two or more per each three-week period and with no seizure-free period > 25 days. The actual mean number of seizures per patient per 28 days during this phase (i.e. baseline) was between 9 and 15 in each treatment group. Key exclusion criteria included clinically significant medical or psychiatric condition or evidence of clinically significant disease, Lennox-Gastaut syndrome, non-motor simple partial seizures only, primary generalised seizures, non-epileptic or psychogenic seizures and seizure clusters in which individual seizures could not be counted. Study endpoints were essentially consistent across the studies. The primary endpoints were the proportional change in seizure frequency per 28 days during the double-blind phase, and the 50% responder rate defined as the proportion of patients who experienced  $\geq 50\%$  reduction in seizure frequency during the maintenance period, both relative to baseline. Secondary endpoints included the Clinical and Patient Global Impression of Change (CGI-C/PGI-C). The primary efficacy endpoint considered for EU registration was the 50% responder rate.

Demographics and baseline characteristics were generally well balanced between treatment groups in each study and consistent with the epidemiology of epilepsy. Across all treatment groups the mean age of patients was approximately 35 years (range 12 to 77 years) and the majority (76%) were female. Patients had a mean duration of epilepsy diagnosis of approximately 21 years. Between 85% and 89% were taking two to three concomitant AEDs, and some patients may also have been treated with concurrent vagal nerve stimulation.

The results for the primary efficacy endpoints were generally consistent between the studies and demonstrated superior efficacy compared with placebo for perampanel at doses of 4 to 12 mg (table 1). In study 304 a statistically significant decrease in seizure frequency was observed for the 8 mg and 12 mg dose when compared with placebo. Although the 50% responder rates were numerically greater in perampanel groups compared with placebo these differences were not statistically significant. However, there was a significant treatment-by-region interaction in this study with an unusually high placebo response seen in Central and South American patients. An analysis of study 304 data from North American sites only found that responder rates were statistically significant for the perampanel 8 and 12 mg groups compared with placebo ( $p \leq 0.05$  for both doses). The magnitude of this treatment effect was consistent with that observed in the other phase 3 studies, further calling into question the observed efficacy in Central and South American patients. Based on sensitivity analyses and additional evidence, European regulators concluded there were 'no uncertainties around the benefits of perampanel in this study'.<sup>8</sup> In study 305 there was a statistically significant decrease in seizure frequency and a significant effect on the 50% responder rate with perampanel 8 and 12 mg compared with placebo. A statistically significant decrease in seizure frequency and a significant improvement in the 50% responder rate were shown for perampanel 4 and 8 mg compared with placebo in study 306. The results for the 2 mg dose were similar to that of placebo. No clear difference in efficacy between perampanel 8 and 12 mg was observed across the studies.

Patient and clinician global assessment scores demonstrated noticeably greater improvements at the greater perampanel doses compared with placebo in each study.

***Pooled analyses***

With similar study designs a pooled analysis of the study results was feasible; the 8 mg dose was included in all three studies, the 12 mg dose was included in two studies, and the 2 and 4 mg doses in a single study. The pooled 50% responder rates were; placebo (19.2%), perampanel 2 mg (20.6%), 4 mg (28.5%), 8 mg (35.3%) and 12 mg (35.1%).

Analysis with Central and South American patients (n = 162) excluded yielded corresponding results; placebo (18.4%), perampanel 2 mg (22.4%), 4 mg (30.8%), 8 mg (37.6%) and 12 mg (39.5%).<sup>16</sup>

***Open-label extension study – Interim results***<sup>14</sup>

A longer-term extension study (study 307) recruited 97% of patients (n = 1,218) from the double-blind phases of the phase 3 studies.<sup>14</sup> This consisted of 380 patients previously randomised to placebo and 838 randomised to perampanel. Of the patients enrolled 1,186 were included for safety analyses and 1,207 in efficacy analyses. Study 307 consisted of two phases; an open-label treatment phase itself consisting of a 16-week blinded conversion period followed by a five-year (256 week) maintenance period, and a four-week follow-up phase. The primary objective was to evaluate the long-term safety and tolerability of perampanel. The secondary objective was to evaluate the maintenance effect of perampanel for the treatment of refractory partial-onset seizures.

Interim results with a cut-off of December 2010 demonstrated that at the end of the 16-week blinded conversion period there was no difference in the median seizure frequency between those patients previously randomised to placebo and those who had continued with perampanel. Both groups demonstrated reductions of about 42% in seizure frequency. This level of seizure frequency reduction was maintained over at least one year of perampanel exposure. Among the 588 patients with at least one year of exposure to perampanel, the median reduction in seizure frequency per 28 days in the last 13-week interval was 47%. In the 19 patients with at least two years of exposure to perampanel the corresponding rate was 56%. In patients with at least one year of exposure to perampanel the responder rate at the end of year one was 48% and in patients with at least two years of exposure it was 63%.

**Table 1.** Summary efficacy outcomes of the three phase 3 studies of perampanel in epilepsy (intention-to-treat analyses) <sup>8,11-13</sup>

	Study 304			Study 305			Study 306			
	Placebo (n = 121)	8 mg (n = 133)	12 mg (n = 133)	Placebo (n = 136)	8 mg (n = 129)	12 mg (n = 121)	Placebo (n = 184)	2 mg (n = 180)	4 mg (n = 172)	8 mg (n = 169)
50% responder rate	26.4%	37.6%	36.1%	14.7%	33.3%	33.9%	17.9%	20.6%	28.5%	34.9%
Difference vs. placebo	-	11.2%	9.7%	-	18.6%	19.2%	-	2.7%	10.6%	17.0%
p	-	0.076	0.091	-	0.002	0.001	-	0.486	0.013	< 0.001
% change in seizure frequency	-21.0	-26.3	-34.5	-9.7	-30.5	-17.6	-10.7	-13.6	-23.3	-30.8
Difference vs. placebo	-	-13.5	-14.2	-	-19.1	-13.7	-	-4.6	-13.7	-20.1
95% confidence interval of difference	-	-26.2 -1.9	-25.0 -2.7	-	-29.2 -8.4	-25.2 -2.3	-	-14.1 -5.2	-23.3 -4.5	-29.7 -10.4
p	-	0.026	0.016	-	0.001	0.011	-	0.420	0.003	< 0.001

**Safety**<sup>11-13</sup>**Phase 3 studies**

During the double-blind phase 3 studies 1,038 patients received at least one dose of perampanel. Overall, perampanel had a favourable safety profile in patients with refractory partial onset seizures with no serious toxicity identified. Safety data pooled from the phase 3 studies show that treatment-emergent adverse events occurred in 77% of patients receiving perampanel versus 67% of placebo patients (table 2). Many of the most common adverse events appear to be dose-related. The most common adverse events were dizziness, somnolence, headache and fatigue. Somnolence appeared to be more frequent during the first few weeks of treatment. Other adverse events reported include ataxia, aggression, anxiety, vertigo, irritability, falls, balance disorder, gait disturbance, dysarthria, blurred vision and increased appetite.

Psychiatric disorders were reported in 15% of patients exposed to perampanel during the phase 3 studies with the most frequently reported psychiatric events being insomnia, anxiety and aggression. Only two cases of suicidal ideation were reported.

More falls occurred in patients exposed to perampanel than placebo. A potential link between falls and the incidence of dizziness and somnolence in patients exposed to perampanel has not been ruled out.

The rate of treatment discontinuations due to adverse events was higher with perampanel 12 mg (19.2%) compared with perampanel 8 mg (7.7%) and placebo (4.5%). The most common cause for discontinuation was dizziness. Convulsions led to discontinuation in a similar proportion of patients in all groups.

The rate of serious adverse events was higher with perampanel 12 mg (8.2%) and 8 mg (5.6%) compared with placebo (5.0%). The only serious events which occurred in more than one patient in any treatment group related to symptoms of epilepsy (e.g. convulsions and status epilepticus). Sudden unexpected death in epilepsy was not observed in the phase 3 studies.

Perampanel does not appear to be associated with any clinically important changes in laboratory values, blood pressure, heart rate, electrocardiography, or neurological or photosensitivity. Perampanel is considered to have a low potential risk for abuse and dependence.<sup>10</sup>

**Open-label extension study (307) – Interim results**<sup>14</sup>

In the open-label extension study the majority of patients (91%) were titrated to perampanel 10 or 12 mg daily. The mean average daily dose was 10 mg. The safety profile of perampanel in patients receiving long-term treatment was consistent with that observed in the phase 3 studies and no new safety signals were identified (table 3). Eighty seven percent of patients reported at least one adverse event and the proportion was similar among those taking one, two or three AEDs at baseline. As the duration of exposure to each perampanel dose varied it was not

possible to determine if the incidence of specific adverse events were dose-related. The only serious adverse events occurring in > 1% of patients were those related to epilepsy. There was one case of sudden unexpected death in epilepsy which was not considered to be related to study treatment.

**Table 2.** Incidence of adverse events, phase 3 studies, pooled data<sup>8,11-13</sup>

	Placebo	Perampanel				
		2 mg	4 mg	8 mg	12 mg	Total
n	442	180	172	431	255	1,038
Any adverse event	294 (67%)	111 (62%)	111 (64.5%)	350 (82%)	227 (89%)	799 (77%)
Event leading to discontinuation	21 (5%)	12 (7%)	5 (2.9%)	33 (8%)	49 (19%)	99 (10%)
Serious adverse event	22 (5%)	6 (3%)	6 (4%)	24 (6%)	21 (8%)	57 (6%)
Adverse events in > 5% (any treatment group)						
Dizziness	40 (9%)	18 (10%)	28 (16%)	137 (32%)	109 (43%)	292 (28%)
Somnolence	32 (7%)	22 (12%)	16 (9%)	67 (16%)	45 (18%)	292 (28%)
Headache	50 (11%)	16 (9%)	19 (11%)	49 (11%)	34 (13%)	118 (11%)
Fatigue (not reported in study 304)	16 (5%)	8 (4%)	13 (8%)	36 (12%)	20 (17%)	77 (7%)

**Table 3.** Incidence of adverse events, long-term open-label extension study (307)<sup>14</sup>

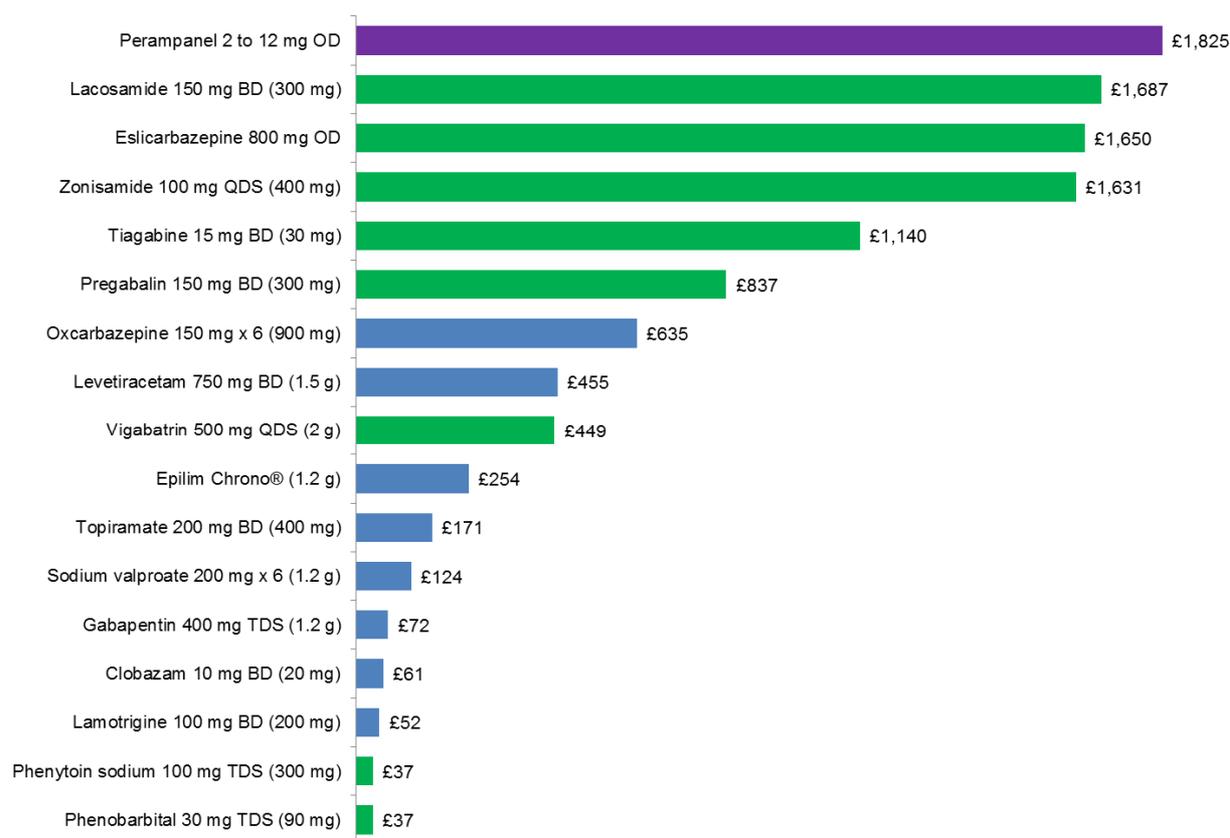
Max daily dose of perampanel	4 mg	> 4 to 8 mg	> 8 to 12 mg	Any
n	15	86	1,084	1,186
Any adverse event	13 (87%)	83 (97%)	940 (87%)	1,037 (87%)
Event leading to discontinuation	6 (40%)	23 (26.7%)	127 (12%)	157 (13%)
Serious adverse event	2 (13%)	11 (12.8%)	144 (13%)	157 (13%)
Adverse events occurring in > 10% of patients (safety analysis set)				
Dizziness	9 (60%)	51 (59%)	461 (43%)	521 (44%)
Somnolence	3 (20%)	23 (27%)	214 (20%)	240 (20%)
Headache	2 (13%)	24 (28%)	172 (16%)	198 (17%)
Fatigue	2 (13%)	13 (15%)	128 (12%)	143 (12%)

## Cost analysis

Costs do not include VAT unless otherwise indicated.

Perampanel is available in packs of 4, 6, 8, 10 or 12 mg tablets each containing 28 tablets. Perampanel 2 mg tablets are available in a pack of 7 tablets. Irrespective of the tablet strength, the cost of perampanel is £5 per tablet.<sup>17</sup> As the range of tablets available covers all licensed treatment doses and the minimum licensed dose titration increment<sup>10</sup> with a single tablet this analysis will assume that patients are treated with one tablet daily. Therefore the cost per patient is £1,825 per annum. This cost is greater than other recommended 2<sup>nd</sup> and 3<sup>rd</sup> line or adjunctive treatment options for partial (focal) seizures<sup>6</sup> at typical doses (figure 1).<sup>18</sup> However the cost of other treatments is variable dependent on the actual dose prescribed. This would not arise with perampanel due to the fixed cost irrespective of the actual dose (assuming one tablet daily). For example, the maximum licensed dose of zonisamide is 500 mg daily<sup>18</sup> which costs £2,044 per patient per annum.<sup>17</sup>

**Figure 1.** Annual treatment costs per patient for 2<sup>nd</sup> and 3<sup>rd</sup> line or adjunctive treatments for partial (focal) epilepsy, correct as of July-Sept 2012.



Doses do not imply therapeutic equivalence. Values are derived for average daily quantities<sup>19</sup> where available, otherwise from the British National Formulary.<sup>18</sup> Blue bars represent 2<sup>nd</sup> line and green bars represent 3<sup>rd</sup> line treatment or adjunctive treatment options for partial (focal) epilepsy.<sup>6</sup>

Although perampanel has demonstrated efficacy in refractory focal epilepsy in combination with other AED, the comparisons were all against placebo. Therefore it is not currently possible to determine the comparative or incremental efficacy of perampanel with other 2<sup>nd</sup> and 3<sup>rd</sup> line treatment options. The volume and nature of the clinical evidence and the cost of treatment may rationally lead to perampanel being considered as a potential 3<sup>rd</sup> line treatment or adjunct such as those indicated in green in figure 1.

For the purposes of a cost-effectiveness calculation the responder rates, defined as the proportion of patients who achieved at least a 50% reduction in seizure frequency compared with baseline (i.e. pre-treatment with perampanel), in the phase 3 studies all yielded similar values of about 35% at typical maintenance doses of 8 to 12 mg daily (i.e. number-needed-to-treat for one 'responder' is three). Therefore the cost per responder is estimated at about £5,200 per responder per annum. However, in practice patients who do not demonstrate an adequate treatment response would discontinue treatment thus reducing the cost per responder per annum. Therefore this value should be interpreted as a likely maximum cost-effectiveness value.

The three most recent drugs licensed and included in the NICE clinical guidance for partial onset seizures<sup>6</sup> are zonisamide (June 2005), lacosamide (September 2008) and eslicarbazepine (October 2009).<sup>20</sup> All three drugs are licensed only for partial onset seizures in age-restricted populations and are available within local formularies. In addition, zonisamide is also licensed for use as monotherapy. Taking typical adult maintenance doses<sup>18</sup> the quantities dispensed within NHS North East primary care between August 2011 and July 2012 (most recent continuous 12 month period for which data is available)<sup>21</sup> indicate about 100 patients using zonisamide, 85 patients using lacosamide and 40 patients using eslicarbazepine. If perampanel was to accrue a similar number of patients as lacosamide (n = 85) after a similar period of time (four years) the equivalent annual cost would be about £155,000 per annum. For comparison, expenditure on lacosamide is currently about £135,000 per annum. This compares with a total spend within NHS North East on drugs used for the 'control of the epilepsies' (BNF section 4.8.1)<sup>18</sup> over the same 1-year period of nearly £22 million.<sup>21</sup> Note that many drugs used for epilepsy are also used extensively for other indications and this expenditure will be included in the stated figure. Prescribing of drugs from secondary care (specialist) locations will not be included in this data. Stated cost values are 'net ingredient cost' which are usually slightly greater than those which are actually reimbursed.

With respect to retigabine, which is not included in the NICE clinical guideline,<sup>6</sup> the cost is about £1,500 per patient per annum<sup>17</sup> at a dose of 900 mg daily (usual maintenance range 600 mg to 1.2 g daily).<sup>18</sup> At maximum licensed dose the cost is about £1,700 per patient per annum. Primary care prescribing of retigabine within NHS North East is currently at very low levels indicating few patients.

## Points to consider

Perampanel is a novel first-in-class oral once-daily drug licensed for the adjunctive (i.e. 'add-on') treatment of partial-onset epilepsy in patients aged from 12 years. The majority of patients (91%) were titrated to treatment doses of 10 or 12 mg daily in phase 3 clinical studies with about 12 month's follow-up.

Perampanel has been evaluated in three robust phase 3 studies which demonstrated consistent efficacy outcomes with up to about eight month's follow-up. Perampanel reduces seizure frequency by > 50% in about 35% of patients and provides mean reductions of about 30% in seizure frequency. One of the key phase 3 studies did not demonstrate a statistically significant benefit for perampanel compared with placebo in one of the primary outcome measures.<sup>11</sup> Emerging longer term evidence indicates that initial efficacy is maintained.

Adverse events associated with perampanel are common and mainly mild to moderate in severity. The most frequently observed adverse events in phase 3 studies (approximate incidence rates in phase 3 studies at typical maintenance doses) were dizziness (about 30 to 40%), headache (about 12%), somnolence (about 15 to 20%), irritability, fatigue (about 15%), falls, and ataxia. Many patients in the phase 3 studies were taking other anti-epileptic drugs and adverse event rates in placebo groups were also high.

Perampanel is not associated with any additional, onerous or exceptional monitoring requirements compared with other anti-epileptic drugs.

Perampanel costs £5 per tablet irrespective of tablet strength. As the available tablets cover all licensed doses in a single tablet it is assumed that a patient can obtain their dose from one tablet daily, yielding a cost of £1,825 per patient per annum. This value is slightly greater (about 10%) than estimated mean treatment costs for other newer anti-epileptic drugs recommended for partial seizures. However the cost of perampanel is insensitive to the dose prescribed whereas other drugs will vary in cost depending on the actual dose.

Based on the uptake within NHS North East of other recent drugs licensed for partial seizure epilepsy the uptake of perampanel is expected to be low, perhaps achieving 85 patients after four years at an annual cost of about £150,000.

## Author's declaration

The lead author has no relevant interests to declare. The report editor (WH) has received remuneration for participation in an advisory board regarding perampanel.

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