NICE advice

Partial-onset seizures in epilepsy: perampanel as adjunctive treatment

Evidence summary
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Overview

The content of this evidence summary was up-to-date in December 2012. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Key points from the evidence

Perampanel is a first-in-class selective, non-competitive antagonist of the AMPA glutamate receptor. It is licensed for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in people aged 12 years and older with epilepsy.

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (NICE clinical guideline 137) recommends carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment if monotherapy is ineffective or not tolerated. If adjunctive treatment is ineffective or not tolerated, the guideline recommends that advice should be sought from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered by the specialist at this point in the care pathway are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide, and retigabine (as recommended in Retigabine for the adjunctive treatment of adults with partial onset seizures in epilepsy with and without secondary generalisation [NICE technology appraisal guidance 232]).

In clinical studies, adjunctive treatment with perampanel 4 to 12 mg once daily has been shown to reduce seizure frequency in people aged 12 years and older with partial-onset seizures and a baseline median seizure frequency ranging from 9.3 to 14.3 per 28 days. In 2 phase III studies (n=386 and n=706, follow-up 19 weeks), seizure frequency decreased by at least half in 33.3% and 34.9% of patients taking perampanel 8 mg daily, compared with 14.7% and 17.9% of patients taking placebo. A third study (n=388, follow-up 19 weeks) did not show a statistically significant reduction in seizure frequency. However, the European Medicines Agency concluded that this was due to regional differences in placebo response and concomitant use of enzyme-inducing anti-epileptic drugs in patients recruited to the trials, and does not suggest a lack of efficacy in European populations (see Clinical effectiveness).

A number of adverse events (78.2% of 1186 patients in an open label extension study) were associated with perampanel treatment, and many appeared to be dose related. Central nervous system adverse events such as dizziness, somnolence, headache and fatigue were seen most commonly. The long-term adverse effects of perampanel are unknown.

Local decision makers will need to consider the place of perampanel alongside the use of other available adjunctive treatments for partial-onset seizures. It is unclear how perampanel compares with other drugs used at this stage in the care pathway. Specialists have suggested that perampanel is an option for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in people aged 12 years and older with epilepsy, when standard adjunctive treatment (with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate) has not provided an adequate response, or has not been tolerated.

Key evidence

French JA, Krauss GL, Biton V et al. (2012) Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 79: 589–96

French JA, Krauss GL, Steinhoff BJ et al. (2012) Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. Epilepsia doi: 10.1111/j.1528-1167.2012.03638.x

Krauss GL, Serratosa JM, Villanueva V et al. (2012) Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 78: 1408–15

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be

of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Relevance to NICE guidance programmes

Perampanel was not considered appropriate for a NICE technology appraisal and is not currently planned within any other NICE work programme.

Introduction

Epilepsy is a common neurological condition characterised by recurring seizures[1]. Epileptic seizures can be broadly categorised into 2 main types: partial and generalised. Partial-onset seizures (also known as 'focal' seizures) are epileptic seizures in which the neuronal discharge begins in, or is restricted to, a localised part of the brain. Generalised seizures are characterised by more diffuse neuronal discharges involving both hemispheres of the brain at the same time[2].

Epilepsy has been estimated to affect 260,000 to 416,000 people in England and Wales, 55% of whom have partial-onset seizures. It has been estimated that recurrent seizures could be controlled with anti-epileptic drugs in approximately 70% of people with active epilepsy, but only 52% of people are seizure free in clinical practice[2].

The NICE clinical guideline on epilepsy advises that people with newly diagnosed partial-onset seizures should be offered monotherapy with carbamazepine or lamotrigine as first-line treatment. If carbamazepine and lamotrigine are unsuitable or not tolerated, levetiracetam, oxcarbazepine or sodium valproate is the next treatment option. If the first anti-epileptic drug tried is ineffective, an alternative from these 5 anti-epileptic drugs should be offered[1].

If first-line treatments are ineffective or not tolerated, adjunctive treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate should be offered[1][3]. For the purposes of this evidence summary, these treatments are referred to as standard adjunctive treatment.

If standard adjunctive treatment is ineffective or not tolerated, advice should be sought from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered by the tertiary epilepsy specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide[1][3]

The NICE technology appraisal on retigabine for partial onset seizures in epilepsy recommends retigabine as an option for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate (standard adjunctive treatment) has not provided an adequate response, or has not been tolerated[4].

[1] National Institute for Health and Clinical Excellence (2012) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 137.

[2] National Institute for Health and Clinical Excellence (2010) Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. NICE technology appraisal final scope.

[3] See the relevant summary of product characteristics for licensed indications.

[4] National Institute for Health and Clinical Excellence (2011) Retigabine for the adjunctive treatment of adults with partial onset seizures in epilepsy with and without secondary generalisation. NICE technology appraisal guidance 232.

Product overview

Drug action

The precise mechanism by which perampanel exerts its anti-epileptic effects is not fully understood. It is a first-in-class selective, non-competitive antagonist of the AMPA glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and its activation of AMPA receptors is thought to be responsible for most fast excitatory synaptic transmission in the brain[5]. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thereby exhibit anticonvulsant effects[6].

Licensed therapeutic indication

Perampanel is licensed for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in people aged 12 years and older with epilepsy[5].

Course and cost

Perampanel should be taken orally once daily at bedtime. The summary of product characteristics for Fycompa advises that treatment should be initiated with a dose of 2 mg/day. Based on clinical response and tolerability, the dose may be increased 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 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. The interval between dose increases should be at least 1 week in people who are taking concomitant drugs that shorten the half-life of perampanel and at least 2 weeks in other people[5].

The current NHS cost of all strengths of perampanel (2, 4, 6, 8 and 12 mg) is £140 for 28 tablets (excluding VAT; costs taken from MIMS, November 2012). Based on this, the cost per patient per year is estimated to be £1820. Costs may vary in different settings because of negotiated procurement discounts.

[5] Eisai Ltd (2012) Fycompa summary of product characteristics

[6] European Medicines Agency (2012) European public assessment report: Fycompa

Evidence review

This evidence review is based on 3 phase III studies (304, 305 and 306) with similar designs and broadly similar results (see table 1).

- Design: 3 multi-centred, randomised, double-blind studies.
- Population: a total of 1480 patients (aged 12 years or older) with uncontrolled partial-onset seizures despite prior therapy with at least 2 anti-epileptic drugs. Patients were eligible if they had at least 5 partial-onset seizures without a 25-day seizure-free period during the 6-week pre-randomisation phases of the studies. Median baseline seizure frequency per 28 days ranged from 9.3 to 14.3 (minimum 1.4, maximum 4503.9). During the course of the study all patients were taking stable doses of 1 to 3 other anti-epileptic drugs.
- Intervention and comparison: perampanel at a dosage of 2, 4, 8 or 12 mg once daily for up to 19 weeks, including a 6-week dose titration period and a 13-week maintenance period, compared with placebo.

- Outcome: the primary outcome measures were the percentage of patients experiencing at least a 50% decrease in seizure frequency (for EU registration) and the percentage change in seizure frequency per 28 days (FDA requirement).

Patients in the 3 phase III studies were eligible to enter an open-label extension study (307) primarily designed to evaluate the long-term safety and tolerability of perampanel. Interim results have been published (median duration of exposure 51.4 weeks [range 1.1 to 128.1 weeks])[7] and are included in this evidence summary (see table 2).

Table 1 Summary of studies 304, 305 and 306

	Placebo	Perampanel				Analysis
		2 mg	4 mg	8 mg	12 mg	Difference vs placebo
Study 304 (French et al. 2012)[1]						
Efficacy (primary outcomes) (n=387)[a]						
	n=121			n=133	n=133	
50% responder rate[b]	26.4%			37.6%	36.1%	8 mg: p=0.0760 12 mg: p=0.0914 Not statistically significant
50% responder rate[b] in North American regional subgroup (n=227)	21.9%			40.5%	40.0%	8 mg: -18.6%, p<0.001[c], NNT=5 12 mg: -18.1%, p<0.001[c], NNT=6
50% responder rate[b] in Central and South American regional subgroup (n=160)	33.3%			33.9%	30.2%	8 mg: p>0.51[c] 12 mg: p>0.51[c] Not statistically significant

Median % reduction in seizure frequency	21.0%			26.3%	34.5%	8 mg: -5.3%, p=0.026 12 mg: -13.5%, p=0.016
Safety (n=388)[d]						
	n=121			n=133	n=134	
Treatment-related adverse events	47.9% (58/121)			74.4% (99/133)	80.6% (108/134)	8 mg: 26.5%, NNH=4 12 mg: 32.7%, NNH=3 p values not stated
Adverse events leading to discontinuation	6.6% (8/121)			6.8% (9/133)	19.4% (26/134)	8 mg: 0.2% 12 mg: 12.8%, NNH=8 p values not stated
Study 305 (French et al. 2012)[2]						
Efficacy (primary outcomes) (n=386)[a]						
	n=136			n=129	n=121	
50% responder rate[b]	14.7%			33.3%	33.9%	8 mg: 18.6%, p=0.0018, NNT=5 12 mg: 19.2%, p=0.0006, NNT=5
Median % reduction in seizure frequency	9.7%			30.5%	17.6%	8 mg: 20.8%, p=0.0008 12 mg: 7.9%, p=0.0105
Safety (n=386)[d]						

	n=136			n=129	n=121	
Treatment-related adverse events	47.8% (65/136)			69.0% (89/129)	77.7% (94/121)	8 mg: 21.2%, NNH=5 12 mg: 29.9%, NNH=3 p values not stated
Adverse events leading to discontinuation	4.4% (6/136)			9.3% (12/129)	19.0% (23/121)	8 mg:4.9%, NNH=20 12 mg: 14.6%, NNH=7 p values not stated
Study 306 (Krauss et al. 2012)[3]						
Efficacy (primary outcomes) (n=705)[a]						
	n=184	n=180	n=172	n=169		
50% responder rate[b]	17.9%	20.6%	28.5%	34.9%		2 mg: p=0.486, not statistically significant[c] 4 mg: 10.6%, p=0.013, NNT=9 8 mg: 17.0%, p<0.001, NNT=6
Median % reduction in seizure frequency	10.7%	13.6%	23.3%	30.8%		2 mg: p=0.420, not statistically significant 4 mg: 12.6%, p=0.003 8 mg: 20.1%, p<0.001
Safety (n=706)[d]						
	n=185	n=180	n=172	n=169		

Treatment-related adverse events	31.9% (59/185)	37.2% (67/180)	44.8% (77/172)	56.8% (96/169)		2 mg: 5.3%, NNH=19 4 mg: 12.9%, NNH=8 8 mg: 24.9%, NNH=4 p values not stated
Adverse events leading to discontinuation	3.8% (7/185)	6.7% (12/180)	2.9% (5/172)	7.1% (12/169)		2 mg: 2.9%, NNH=34 4 mg: -0.9% 8 mg: 3.3%, NNH=30 p values not stated

Abbreviations: NNH, number needed to harm; NNT, number needed to treat.

[a] Analysis only included patients who had at least 1 dose of study drug and for whom there was any seizure outcome data (modified intention to treat).

[b] Percentage of patients experiencing at least a 50% decrease in seizure frequency in the maintenance period relative to baseline.

[c] European Medicines Agency (2012) European public assessment report: Fycompa

[d] All patients who had at least 1 dose of study drug. 1 patient randomised to 12 mg perampanel in study 304 and 1 patient randomised to placebo in study 306 were treated for 1 day only and did not complete seizure diaries. They were therefore excluded from the efficacy analyses.

[1] French JA, Krauss GL, Biton V et al. (2012) Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 79: 589–96

[2] French JA, Krauss GL, Steinhoff BJ et al. (2012) Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305. Epilepsia doi: 10.1111/j.1528-1167.2012.03638.x

[3] Krauss GL, Serratosa JM, Villanueva V et al. (2012) Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 78: 1408–15

Table 2 Summary of study 307 (Krauss et al. 2012)[7]

	Perampanel dose				
	2 mg	4 mg	8 mg	12 mg	
Safety (n=1186)					
	<4 mg/day (n=1)	4 mg/day (n=15)	>4 to 8 mg/day (n=86)	>8 to 12 mg/day (n=1084)	Total (all doses, n=1186)
Treatment-related adverse events	0/1	86.7% (13/15)	95.3% (82/86)	76.8% (832/1084)	78.2% (927/1186)
Adverse events leading to discontinuation	100% (1/1)	40.0% (6/15)	26.7% (23/86)	11.7% (127/1084)	13.2% (157/1186)
No placebo comparison available. p values for comparisons not given.					

Clinical effectiveness

Reduction in seizure frequency

Perampanel was shown to be more effective than placebo in reducing the frequency of epileptic seizures at dosages from 4 mg to 12 mg daily, but not at a dosage of 2 mg daily.

Proportion of patients with a 50% or greater decrease in seizure frequency

In study 305, 33.3% of patients taking perampanel 8 mg and 33.9% of those taking perampanel 12 mg experienced a decrease in seizure frequency of at least 50%, compared with 14.7% of patients taking placebo (number needed to treat [NNT] 5).

In study 304, the percentage of patients with a decrease in seizure frequency of at least 50% was 37.6% for patients taking perampanel 8 mg and 36.1% for patients taking perampanel 12 mg, compared with 26.4% of patients taking placebo. These were not significantly different from placebo. However, analysis of responder rates by region showed significant differences from placebo in the North American subgroup but not in the Central and South American subgroup.

Pooled data from studies 304, 305 and 306 indicate that the proportion of patients who had a decrease in seizure frequency of at least 50% was much greater (by 2 to 3-fold) among those taking

perampanel 8 mg or 12 mg daily who were not also taking the enzyme-inducing drugs carbamazepine, oxcarbazepine or phenytoin[8].

In its assessment of perampanel, the Committee for Medicinal Products for Human Use (CHMP) concluded that the regional differences seen in study 304 were due to a high response to placebo and the high concomitant use of enzyme-inducing anti-epileptic drugs in the Central and South American regional subgroup. Results for the North American subgroup were consistent with the other 2 studies, which included European populations[8].

Study 306 did not find a statistically significant difference from placebo in the proportion of patients taking perampanel 2 mg daily who experienced a decrease in seizure frequency of at least 50%. No significant difference in this outcome was seen between the groups taking perampanel 8 mg and 12 mg in studies 304 and 305[8].

Safety

Treatment-emergent adverse events were reported in 87.4% of patients in the phase III studies and the open-label extension study. They were considered to be treatment related in 78.2% of patients and led to discontinuation of treatment in 13.2% of patients[7]. Central nervous system adverse events were seen most commonly (dizziness, somnolence, fatigue, headache, ataxia, aggression, anxiety, vertigo, irritability and falls).

Study results suggest that there is a dose-related increase in adverse events. The summary of product characteristics for Fycompa states that in phase III studies, the rate of discontinuation as a result of an adverse event was 1.7% in patients taking perampanel 4 mg, 4.2% in patients taking 8 mg and 13.7% in patients taking 12 mg, compared with 1.4% in patients taking placebo[9]. For adverse effects leading to treatment discontinuation, this suggests numbers needed to harm (NNH) of 36 for perampanel 8 mg daily and 8 for perampanel 12 mg daily, compared with placebo.

Evidence strengths and limitations

It is unclear how perampanel compares with other drugs used at this stage in the epilepsy care pathway. The European Medicines Agency states that the efficacy of perampanel appears modest in the overall population compared with other recently approved anti-epileptic drugs, although there are no head-to-head data available. Perampanel has demonstrated consistent efficacy as adjunctive treatment for refractory partial-onset seizures with or without secondarily generalised seizures in people aged 12 years and older with epilepsy at dosages of 4 to 12 mg daily[8].

In study 307, improvement in seizure frequency was maintained for up to 2 years. However, this study was open-label, did not include a placebo comparison and patients were able to change their other anti-epileptic drugs, which may have maintained efficacy. It is not known whether the efficacy of perampanel will be maintained in the longer term.

The long-term adverse effects of perampanel are unknown. In all controlled and uncontrolled trials that have been carried out in patients with partial-onset seizures, 1639 patients have received perampanel; of these, 1174 have been treated for 6 months and 703 for longer than 12 months[9].

[7] Krauss GL, Perucca E, Ben-Menachem E et al. (2012) Perampanel, a selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: Interim results from phase III, extension study 307. Epilepsia doi: 10.1111/j.1528-1167.2012.03648.x

[8] European Medicines Agency (2012) European public assessment report: Fycompa

[9] Eisai Ltd (2012) Fycompa summary of product characteristics

Context

Treatment alternatives

Perampanel is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures. The NICE clinical guideline on epilepsy advises that, if standard adjunctive treatment is ineffective or not tolerated, advice should be sought from a tertiary epilepsy specialist. Anti-epileptic drugs that may be considered by the tertiary epilepsy specialist at this stage in the care pathway are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide and retigabine [10],[11],[12].

Costs of treatment alternatives

	Usual adult maintenance dose[1,a]	28-day cost excluding VAT
Eslicarbazepine acetate	800–1200 mg once daily	£126.93 to £190.40[b]
Lacosamide	100–200 mg twice daily	£86.50 to £144.16[c]

Perampanel	4–12 mg once daily	£140[b]
Phenobarbital	60–180 mg once daily	£1.54 to £7.23[c]
Phenytoin sodium	200–500 mg daily in single or divided doses	Tablets: £60 to £150[c] Capsules: £45 to £112.50[c]
Pregabalin	150–600 mg daily in 2 or 3 divided doses	£64.40 to £96.60[c]
Retigabine	600–1200 mg in 3 divided doses	£77.86 to £127.68[b]
Tiagabine	15–45 mg daily in 2 or 3 divided doses	£43.71 to £131.15[c]
Vigabatrin	2–3 g daily	£34.54 to £51.81[c]
Zonisamide	300–500 mg daily	£94.08 to £156.80[c]
[a] The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence. [b] Costs for solid dose forms; taken from MIMS November 2012. [c] Costs for solid dose forms; taken from Drug Tariff November 2012.		
[1] Doses taken from the relevant summary of product characteristics.		

[10] National Institute for Health and Clinical Excellence (2012) The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 137.

[11] See the relevant summary of product characteristics for licensed indications.

[12] National Institute for Health and Clinical Excellence (2011) Retigabine for the adjunctive treatment of adults with partial onset seizures in epilepsy with and without secondary generalisation. NICE technology appraisal guidance 232.

Estimated impact for the NHS

Likely place in therapy

Perampanel is licensed for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in people with epilepsy aged 12 years and older. Specialists have

suggested that perampanel is an option for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in people aged 12 years and older with epilepsy, when standard adjunctive treatment has not provided an adequate response, or has not been tolerated. The NICE clinical guideline on epilepsy advises that treatment options at this point in the care pathway should be made after advice from a tertiary epilepsy specialist. Efficacy, cost, safety and individual patient factors will all influence the decision to use a particular second-line adjunctive anti-epileptic drug in each person. Although no studies are available comparing perampanel with other anti-epileptic drugs, the European Medicines Agency states that the efficacy of perampanel appears modest in the overall population compared with other recently approved anti-epileptic drugs[13].

Estimated usage

The number of people in England and Wales estimated to have epilepsy ranges from 260,000 to 416,000; partial-onset seizures affect between118,800 to 228,800 of these. It has been estimated that recurrent seizures could be controlled with anti-epileptic drugs in approximately 70% of people with active epilepsy[14], which suggests that around 35,640 to 68,640 people in England and Wales have partial-onset seizures that are refractory to current treatment and may benefit from further treatment options. It is not possible to estimate usage of perampanel based on the available data; however, it is likely that it could be used in a proportion of these patients.

[13] European Medicines Agency (2012) European public assessment report: Fycompa

[14] National Institute for Health and Clinical Excellence (2010) Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. NICE technology appraisal final scope.

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For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – interim process statement.

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