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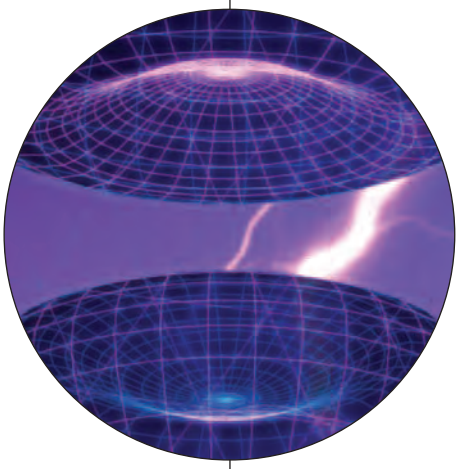
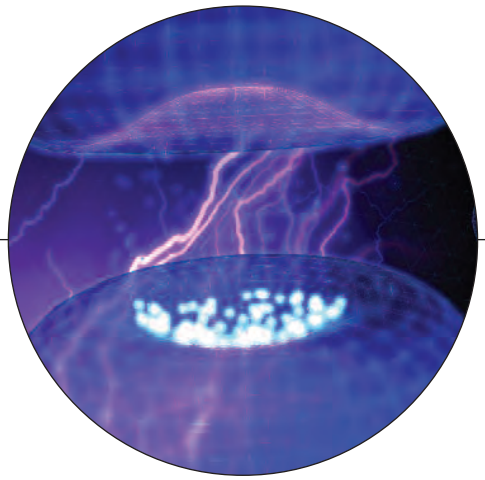
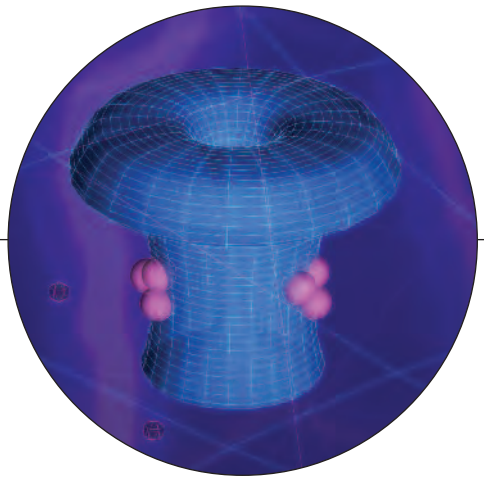


Making a Difference for Patients with Uncontrolled Epilepsy

John J Craig, Mary Parrett, Charlotte Lawthom, J Helen Cross, Philip N Patsalos, John Paul Leach





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Introduction

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Conflicts of interest:
Dr. Craig reports personal fees from UCB Pharma, Sanofi-Synthélabo, GlaxoSmithKline, Janssen-Cilag, Pfizer and Eisai to undertake lectures and participate in advisory boards.

Current treatment landscape

In the UK, epilepsy directly affects over 400,000 people.[1,2] Between 60 and 70% of those diagnosed with epilepsy will become seizure free and achieve long-term remission,[3,4] but many will continue to have seizures in spite of treatment.[4,5]

Drug-resistant or chronic epilepsy, defined by the ILAE as continuing seizures despite effective trials of at least two appropriately selected antiepileptic drugs (AEDs) given in appropriate doses[6] affects around 100,000 people in the UK[1] and has a major impact on many aspects of a patient's life (Figure 1).[1, 7-10]

In the UK, there are around 1,000 deaths a year due to epilepsy, with sudden unexpected death in epilepsy (SUDEP) accounting for half of these.[11] A report from a UK parliamentary debate on the prevention of deaths from epilepsy noted that in the 10 years since the National Sentinel Clinical Audit was conducted, there had been no decline in the number of epilepsy-related deaths each year.[12]

Managing uncontrolled patients: don't give up!

The ILAE definition of chronic epilepsy, if misinterpreted, has the potential to promote reluctance to actively treat patients with epilepsy who have failed two AEDs. However, it seems that such an approach is unnecessarily nihilistic:[13,14] around half of people with apparently drug-resistant epilepsy can experience significant improvements in seizure control with further appropriate drug changes.[15] In patients with uncontrolled disease, active treatment revision could reduce the risk of SUDEP, maximise the potential for seizure freedom and have a positive impact on a patient's quality of life.

Perampanel▼

Despite an increasing number of available treatments for epilepsy, there is a need for more effective AEDs. Perampanel, with its novel MOA, is an interesting addition to these therapeutic options and offers hope in treating uncontrolled patients. Perampanel selectively targets post-synaptic glutamate receptors, and in particular AMPA-receptor-mediated fast excitatory neurotransmission.[16] It has minimal affinity for receptors other than the AMPA receptor and is therefore less likely to have the neurobehavioural side effects that are specific to NMDA receptor antagonists. Perampanel has been shown to demonstrate anti-seizure activity in a wide range of animal models.[17] It has proven efficacy in partial onset seizures with secondary generalisation and is approved for use in children (>12 years) as well as adults. It is well tolerated and with a long half-life and simple titration schedule is easy to use and take.

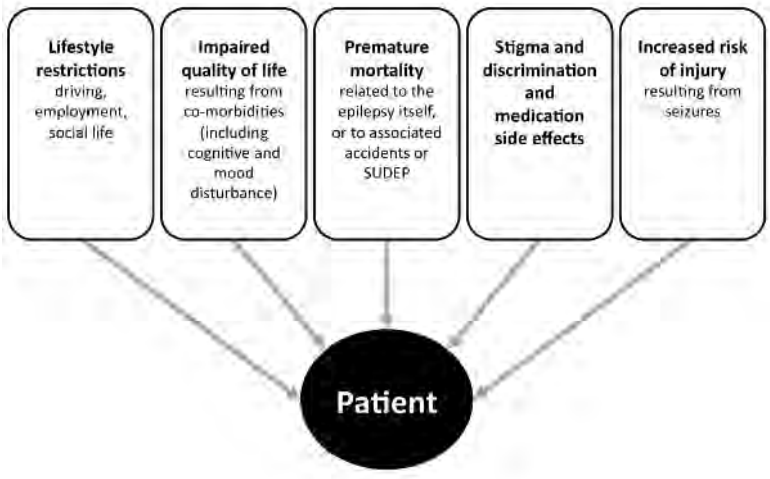

Figure 1 The impact of epilepsy on patients' lives

Efficacy and safety data for perampanel have been provided from three phase III studies (304[18], 305[19], 306[20]) that enrolled 1478 subjects of ≥12 years with ≥5 seizures in a six week period and who were being treated with one to three other AEDs.[21] Overview and study designs (including the open-label extension study (OLE) 307[22]) are shown in Figure 2.

The primary efficacy end point in the three studies was the percentage of patients achieving a 50% reduction in the frequency of all partial seizures per 28 days (50% responder rate; baseline vs. maintenance).[21] The median percentage changes in the frequencies of complex partial plus secondarily generalised seizures, and secondarily generalised seizures only were assessed as secondary end points. Safety endpoints were determined by measuring treatment-emergent adverse events (TEAEs), vital signs, and changes in clinical laboratory parameters and ECGs.

Patient demography and clinical characteristics were similar across the pivotal phase III studies and treatment groups and perampanel doses. In a pooled analysis of the three studies,[21] TEAEs necessitated withdrawal of perampanel in 99 patients (9.5%) overall, and 19.2% of patients in the 12mg group (n=49). For the adolescent and adult patients studied, significant reductions in the frequency of all partial seizures were found, especially for those with secondarily generalised seizures. Most adverse events (AEs) were considered mild to moderate in severity including neurobehavioural AEs. No clinically important changes or treatment group differences in vital signs, ECG recordings or haematological or biochemical parameters were noted. Weight increase (>7%) was, however, seen in 14.6% of perampanel-treated patients compared with 7.1% of placebo-treated patients.

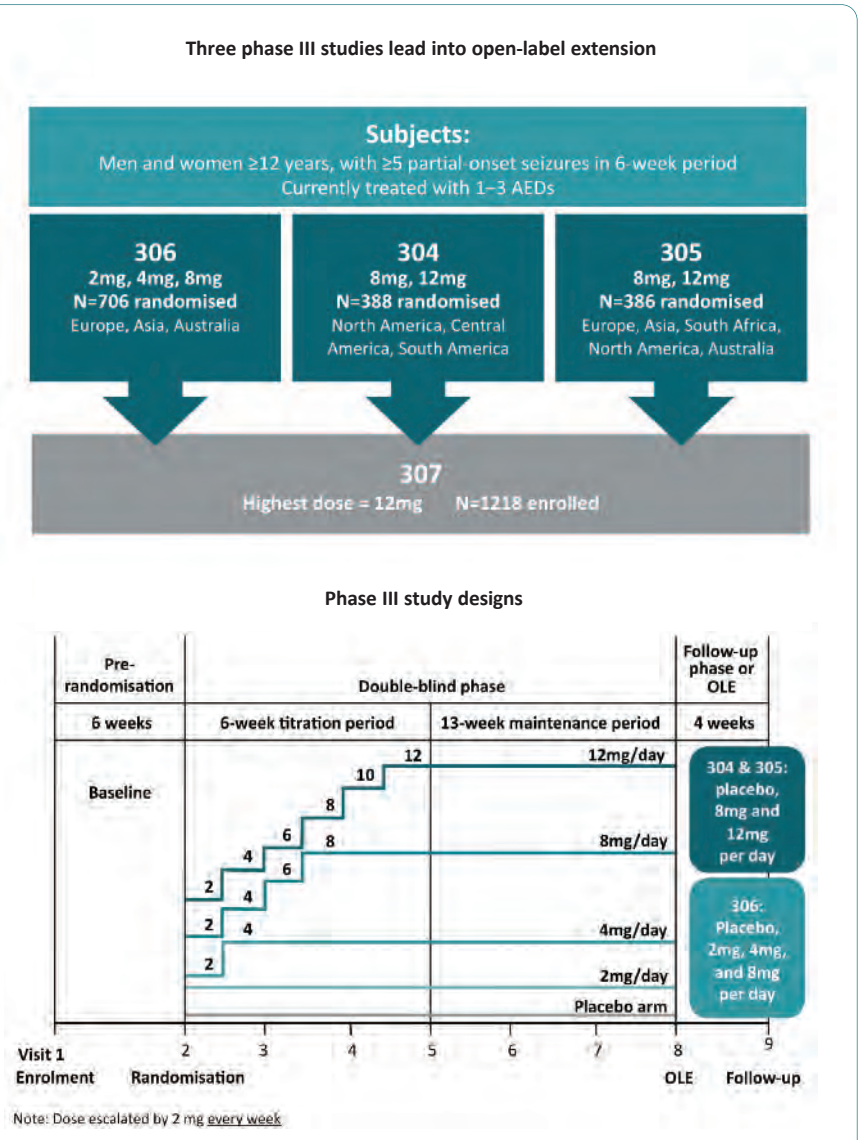

Figure 2 Overview and study designs for perampanel phase III and OLE studies[18-22]

Conclusion

Perampanel, which has been licensed for one year, is being used for adjunctive treatment in those with focal onset seizures, with or without secondary generalization. By April 2013, it was estimated that around 2,000 patients from the UK (~7,000 worldwide) have been treated with perampanel.[23] In this supplement we will review the experience with perampanel to date from individuals with expertise in managing patients with epilepsy. Each article will concentrate on a specific aspect of epilepsy management and will illustrate the relevant aspects through the use of case studies.

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My experience with perampanel

Mary Parrett

is the Clinical Nurse Specialist (Sapphire Nurse) in Epilepsy at the Royal Cornwall Hospital. She set up the service in Cornwall in 1998 initially funded by Epilepsy Action as part of their "Sapphire Nurse Scheme". Previously a Neurology Ward Manager and ED team leader, Mary gained experience in both these areas which sparked an interest in the condition and highlighted the then unmet need for support for those living with epilepsy or affected by it.

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Conflicts of interest:
Ms Parrett reports honoraria from Eisai and GlaxoSmithKline to undertake educational presentations at conferences and GP meetings, and to participate in advisory boards.

In my clinical practice as a specialist epilepsy nurse, I have encountered many patients who struggle not just with the diagnosis of epilepsy but also in coping with ongoing seizures. They may have tried and failed multiple AEDs (due to lack of efficacy or tolerability issues) and lost hope of achieving seizure freedom. Epilepsy impacts on their quality of life and they struggle with not knowing if/when the next seizure will happen, and how bad this will be.

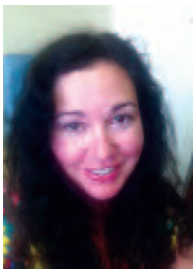
Perampanel offers a novel mode of action and simple titration schedule for patients with uncontrolled epilepsy. Perampanel is initiated with a dose of 2mg/day and titrated with increments of 2mg/day no more frequently than every 2 weeks; the exception to this is when perampanel is taken concomitantly with drugs that shorten the half-life of perampanel, in which case it should be titrated no more frequently than at 1-week intervals. In my experience, perampanel is well tolerated and efficacious even in the most complex cases. Perampanel has had a positive impact on seizures in many of my patients, resulting in improved confidence and self-esteem. The average half-life of 105 hours gives me some confidence that if a patient inadvertently misses a dose, the therapeutic effect may be maintained until the next scheduled dose, although patients must always be encouraged to adhere fully to their treatment regimen.

As perampanel is given as a single daily dose, the potential impact of dizziness may be minimised by taking the dose at bedtime. My patients have found bedtime dosing is convenient to remember and I believe that timing dosing in this way may aid compliance. These patients report that the small 'film-coated' tablets are easy to take. This is particularly relevant for those with swallowing difficulties, or for young people (perampanel is licensed for patients ≥12 years).

Perampanel therefore offers advantages for patients who struggle with ongoing seizures and remembering to take medication, and who have tried other AEDs without benefit. Patients and practitioners appreciate the flexible titration schedule and the simple dose increases. Perampanel treatment has significantly reduced seizure events in those with partial onset seizures and secondary generalised tonic–clonic seizures. Furthermore, treatment success has been maintained over time, with some adjunctive medications being successfully reduced or removed without negative effect. Overall, for the patients I have supported, my early experience with perampanel has been encouraging and this drug has provided a useful addition to the AEDs available.

Case study 1

A 27-year-old woman with a young child developed epilepsy at 18 years of age (bilateral periventricular heterotopia, with abnormal foci). She experienced four complex partial seizures per month with occasional secondary generalised tonic–clonic seizures (2 in 3 months) and had failed many previous AEDs at maximum doses (lamotrigine, eslicarbazepine acetate, pregabalin, lacosamide, zonisamide). She had a history of mood swings with carbamazepine, drowsiness on topiramate and weight gain on pregabalin. Her primary goal was complete seizure seizure freedom because she is a mother of a young child: she wanted a well-tolerated agent, that was easy to take, and which would reduce/eliminate both the complex partial seizures and the secondarily generalised tonic–clonic seizures. Perampanel was selected because of its efficacy for both complex focal seizures and secondarily generalised seizures, and its ease of use. She started perampanel concomitant with clobazam (60mg total daily dose) and levetiracetam (3000mg total daily dose) with cautious titration of perampanel because of tolerability issues with previous AEDs (2mg increase every month) to 12mg. Perampanel treatment resulted in a great improvement in seizures, with only occasional complex partial seizures at the 12mg dose (<1/month). In this patient, perampanel was well tolerated and taken to a maximum dose on a monthly titration regime. Perampanel was effective where many pre-synaptic AEDs had not shown efficacy.



Charlotte Lawthom

is a Consultant Neurologist in Newport, South Wales. She is interested in clinical innovation and team working and has recently won an award for developing an open access epilepsy service. Her research interests dovetail with this clinical pragmatism and she is currently active in pharmacology research. Previous research in SUDEP and a PhD investigating visual loss with vigabatrin use remain ongoing areas of clinical and research development. She is also a keen clinical teacher and is interested particularly in the impact of mentoring.

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Conflicts of interest:
Dr Lawthom has received speaker fees from GlaxoSmithKline, UCB and Eisai in the past three years, as well as advisory board fees from Eisai.

Efficacy of perampanel for complex partial seizures and secondarily generalised seizures

Perampanel arrived at the tail end of a flurry of new antiepileptic drugs (AEDs). An initial glance at the trial data reveals a very familiar design of three phase III global studies feeding into an open-label extension,[1] albeit with the difference of inclusion of children (≥12 years).[2] Closer inspection of the pooled analysis of phase III data reveals a highly uncontrolled group of individuals with epilepsy; with baseline seizure frequencies of 10 to 13 per month and with 32.2-38.9% of participants on three other baseline AEDs across the studies, and a further 44.4-56.9% on two AEDs.[2] Many patients (63.9-71.9%) had secondarily generalised seizures at baseline.[2] Patients also had a long duration of epilepsy (19.7-22.6 years) and a proportion had undergone prior epilepsy surgery (12.0%) or had used a vagal nerve stimulator (6.3%).

Considered in this context, the data is more encouraging than might have been expected. The pooled phase III data for the standard seizure responder rates (>50% reduction in seizures) ranged from a maximum of 35.3% for all seizures, to a maximum of 60.5% for secondary generalised seizures.[2] Some patients fared particularly well on perampanel, with up to 17.4% and 46.5% achieving a >75% reduction in all seizures and secondary generalised seizures, respectively.[2,3] Median percentage seizure change data were similar (Figure 1 overleaf).[2]

Seizure-freedom rates for all seizure types were up to 4.4%.[2] The high response rate for secondary generalised seizures was further underlined by the seizure-freedom rate for secondary generalised seizures of perampanel 8mg (28.9%; $p<0.01$) and 12mg (27.0%; $p<0.05$) as compared with placebo (14.2%).[3]

The limitations of short-term trial data are well recognised. Arguably more pragmatic information might be forthcoming from the open-label extension study.[4] Pooled data from this study demonstrate the responder rate for all seizures was 46.9% at 1 year. The patient retention rate of 70.8% at 1 year suggests good tolerability.[4] The rates of total seizure freedom in this study are promising: of the patients with 6 months of data (n=586), 16.4% were seizure free for the last 3 months and 8.9% for the entire 6 months. For the patients with 9 (n=410) and 12 (n=238) months of data, the seizure-free rates for the entire 9 or 12-month period were 7.6% and 7.1%, respectively.[4]

Initial experience in our centre has mirrored the trial data; perampanel has been well-tolerated in patients with difficult-to-treat epilepsy. We have seen a significant reduction in all seizures but with the most noticeable impact on secondary generalised seizures.

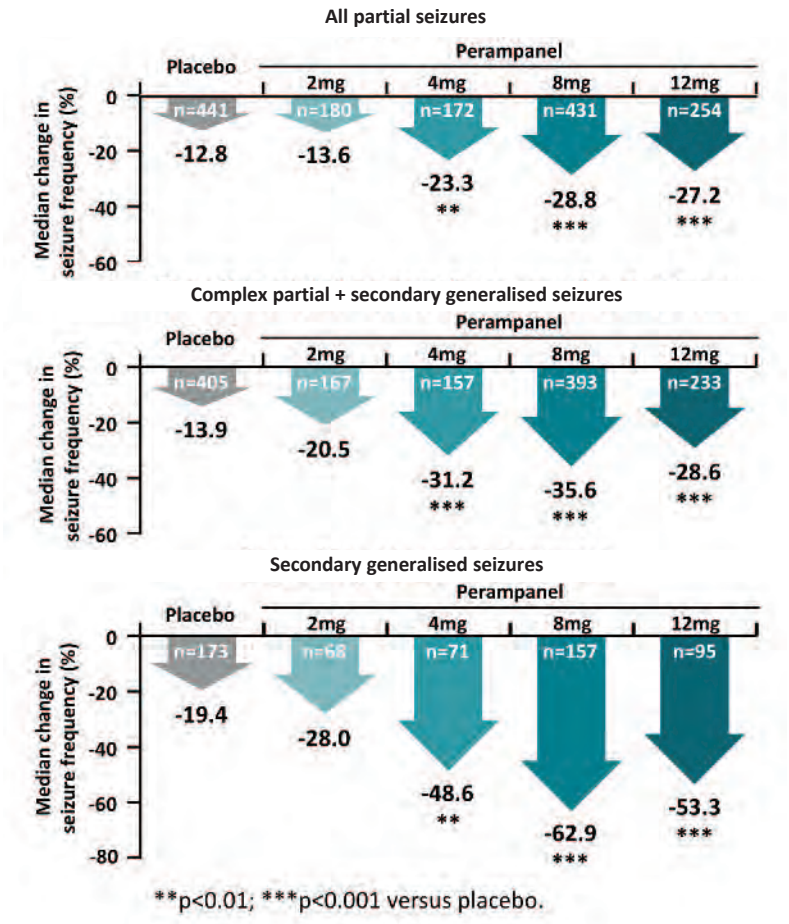

Figure 1: Median percentage changes in the frequencies of seizures between baseline and double-blind treatment phase (ITT analysis set, pooled phase III analysis)[2]

Case study 2

A 52-year-old woman with cerebral palsy and moderate learning difficulties was first diagnosed with focal onset epilepsy in 2010. She presented with status epilepticus and then had non-convulsive status epilepticus. She experienced frequent seizures, with both simple and complex partial seizures occurring on a daily basis as well as secondarily generalised tonic–clonic seizures occurring weekly. Low mood has been an ongoing problem. Since the patient had tried multiple previous AEDs and was experiencing escalating secondarily generalised tonic–clonic seizures, she was prescribed perampanel. The dose was commenced at 2mg and titrated by 2mg weekly (as per the Summary of Product Characteristics titration guidance, because carbamazepine shortens the half-life of perampanel) up to 10mg. Concomitant medications comprised carbamazepine 600mg daily, phenytoin 450mg, eslicarbazepine acetate 1200mg, levetiracetam 3000mg (1500mg twice daily), clobazam 10mg as needed and citalopram 10mg for depression. The patient has been free of secondarily generalised tonic–clonic seizures since commencement of perampanel and the frequency of partial seizures has decreased significantly from daily to monthly, with no reported adverse events to date. Along with the reduction in seizures, she has regained her social activities and has also regained her previous ability to undertake standing transfers, resulting in an improvement in her overall quality of life.

Whilst seizure freedom is the ultimate goal in any patient, it is the frequency of seizures that determines risk of Sudden Unexpected Death In Epilepsy (SUDEP) – the more frequent the seizures, the higher the risk.[5] The inherent risks associated with SUDEP, along with other traumatic harm in secondary generalised seizures, is a major consideration in epilepsy management.[3]

Although there is little comparative data for the impact of newly available AEDs on secondary generalised seizures, the data on efficacy of perampanel for secondarily generalised seizures are encouraging. Whilst some of this might be explained by ascertainment bias, it is noteworthy that AMPA receptors are primary modulators of seizure spread.[6] Further, AMPA receptors demonstrate hypersensitivity in epileptogenic areas. Perhaps then, it is unsurprising that perampanel might reasonably target epileptogenic areas and prevent secondary generalisation.

As with all drugs, confidence comes only with the passage of time. A three-year experience of nine patients aged 12 years and above has been reported in Canada.[1] Eight patients remain on the drug, with two remaining seizure free and six experiencing only rare disabling seizures. UK-based data may be slower to materialise. As a nation, we practise cautious and conservative medicine and even in the high-risk setting of highly refractory epilepsy this maxim holds true.

Interest in perampanel is growing in the epilepsy community in the UK. A multi-site audit of perampanel usage has already recruited over 120 patients. A single-site audit aims to recruit several hundred patients. Whilst the novel mode of action of perampanel might attract epileptologists, continued uptake will only occur in the setting of perceived efficacy and tolerability.

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Managing side effects of perampanel

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Conflicts of interest:
Professor Cross holds an endowed Chair through the University College, London. She has sat on Advisory Panels for Eisai and ViroPharma for which renumeration has been paid to her department. She currently holds grants for research as Co-Investigator from Action Medical Research, Epilepsy Research UK, Great Ormond Street Hospital Children's Charity, and the European Commission. She works as Clinical Advisor to Children's Epilepsy Surgery Service for which renumeration was made to her department.

On evaluating the use of any AED, it is important to consider the possible side effects, and counsel patients accordingly of what they might expect. Only a minority of individuals experience significant side effects; it is important to warn patients and families of the possibility of such and the likely symptoms that may be experienced. Such side effects may not necessarily require discontinuation of a medication; clinical experience is likely to then determine the most appropriate way to avoid such effects.

In the first instance, regulatory trials can be scrutinised for the likely side effects an individual may experience. Data from five such trials of perampanel are available; three randomised controlled phase III trials (cumulative total of 1,491 patients)[1-3] and two open-label trials, one an extension (1,218 patients) of the three RCTs[4] and one open-label extension from phase II trials (138 patients).[5] The most frequent (occurring in >10% of patients in any treatment group) treatment-emergent side effects in the RCTs were dizziness, somnolence, fatigue, and headache, with an apparent dose effect suggested for all except headache. Two trials are identical in methodology examining 8mg vs 12mg vs placebo in differing populations;[1,2] one trial compares three dosing regimes (2mg, 4mg and 8mg).[3] In the latter study, dose reduction or interruption due to treatment-emergent adverse events (TEAEs) was far more likely to occur at the higher dose, (8mg 17.2%) than at a lower dose (2mg 1.7%) confirming the likely dose effect.[3] In study 304, psychiatric serious AEs overall had a higher rate in the 12mg group (3.7%) than the 8mg (<1%) or placebo (1.7%) groups. In study 305, also comparing 8mg vs 12mg vs placebo, psychiatric AEs occurred more frequently in the 12mg perampanel group (17.4%) than the 8mg perampanel group (14.0%) or placebo (14.0%).[2] In a post hoc analysis of pooled study data by randomised dose, TEAEs necessitated withdrawal of perampanel in 99 patients (2mg 6.7%, 4mg 2.9%, 8mg 7.7% and 12mg 19.2% compared to 4.8% in the placebo group).[6]

Study 307 (open-label data) enrolled 1,218 patients, of whom 1,186 were included in the safety analysis. 580 (48.9%) patients had more than one year of exposure to the medication, and 19 (1.6%) patients had more than two years.[4] At the interim analysis, 840 (70.8%) patients remained on perampanel treatment. The large majority of patients (n = 1,084 [91%]) were titrated to a higher dose, namely 10mg or 12mg/day. TEAEs were reported in 87.4% of patients, most frequently dizziness (43.9%), somnolence (20.2%), headache (16.7%), and fatigue (12.1%). Serious adverse events were reported in 13.2% of patients. TEAEs related to depression were reported in 59 (5.0%) patients. Anxiety and confusional state were reported in 46 (3.9%) and 20 (1.7%) patients, respectively. In the smaller open label-study following the phase II trials, 138 of 180 individuals enrolled in the open-label evaluation.[5] At interim analysis, 41.3% had more than three years' exposure. As demonstrated in the RCTs, the most common adverse events were dizziness, somnolence and headache, with dizziness leading to withdrawal of the medication in 3 patients. Anxiety was the only psychiatric TEAE occurring in over 5% (7.2%).

Caveats in reviewing this data have to be highlighted however. Follow-up in RCTs is only short term, and even in the open-label studies data are limited with regard to side effects. Rare but significant side effects may not reach a threshold for reporting. Post-licensing data is equally important in determining what individual side effects may be experienced, what long-term surprises may appear and therefore continued reporting and discussion of clinical experience is imperative. However, some clues of what to expect with the medication can be gained and consequently how to manage such. The clinical cases reported within this supplement provide interesting food for thought. Currently we are limited in the dosing we can utilise, particularly in the younger population. In case study 3 (overleaf) 'dizziness', known to be a significant reported adverse event in the trials, was troublesome. By simple re-timing of administration to immediately before sleep this was resolved. Peak plasma level for perampanel has been determined to be between 0.25 and 2 hours,[7] despite its relatively long half-life, so these observations would be in keeping with this.

There is a high rate of behaviour/psychiatric disorder in adults and children with complex, refractory epilepsy.[8,9] It is known that treatment may be associated with exacerbation of such problems, whether the direct effect of treatment or the result of the effect on seizures. Physicians may therefore be wary of trialling a medication with a history of behavioural effects in a patient with known associated problems. Case study 4 (overleaf) illustrates that despite the reports of treatment-emergent psychiatric problems in pivotal clinical trials, perampanel improved management of seizures, which lead to an improvement of behaviour.

References overleaf >

Case study 3

A 16-year-old girl experienced epilepsy characterised by seizures with occipital lobe semiology. She had normal cognition (FSIQ 99) but some specific difficulties affecting language and verbal memory. She had her first seizure aged 8 years, and subsequent seizures occurred every two weeks. Aurae with visual features occurred around 6 times a day. Longer focal seizures, which occurred 1–2 times a week, could be prolonged and included altered awareness, and up to twice per week evolved to bilateral convulsive seizures (secondary generalisation). Her epilepsy was drug-resistant. Previous failed treatments included carbamazepine, topiramate, oxcarbazepine, levetiracetam, sodium valproate, clobazam, lamotrigine, and the ketogenic diet. A partial response was seen with vagus nerve stimulation therapy. Pre-surgical evaluation is ongoing. Perampanel was added to lamotrigine 100mg twice daily and the dose was increased every 2 weeks to a maximum dose of 12mg nocte. She experienced a response from 6mg, with abolition of escalation to secondarily generalised seizures. There was no change to the frequency of aurae with visual features or prolonged focal dyscognitive seizures. The perampanel dose is currently being titrated down to look for the minimum effective dose. She had significant dizziness with the 4mg dose which began 20 minutes after the dose was taken at 7pm. Dizziness was overcome by taking the dose in bed before sleeping. In this patient, the side effect of dizziness was real but there are clear strategies to overcome it.

Case study 4

A previously well 16-year-old boy had encephalitis at age 4 resulting in severe developmental delay, severe learning difficulties and aggressive behaviour. He had 0-5 focal seizures per day on 10-30 days a month; the focal seizures occurred with or without secondarily generalisation. He had aggressive outbursts particularly on days when he had seizures. Diagnostic tests (EEG, MRI and PET) indicated lesion negative right fronto-temporal focal epilepsy. Previous interventions included 13 appropriate AEDs and the ketogenic diet. His parents were not keen for vagal nerve stimulation therapy. This was therefore a medically difficult-to-treat epilepsy. Perampanel was initiated due to his ongoing seizures and because it was compatible with his concomitant AEDs, lacosamide and clonazepam. Perampanel was initiated at 2mg (bedtime dose) and the dose increased to 4mg after two weeks and 6mg after a further 4 weeks. The patient responded well: at three months, his seizures reduced to 0-3 per day on 5-10 days a month and the focal seizures were shorter and less severe, with none occurring during the night and fewer secondarily generalised seizures. He remained seizure free for 21 days at 4mg. Perampanel was well tolerated with no reported side effects to date. Importantly, his aggressive behaviour and overall behaviour noticeably improved in parallel with improved seizure control, and consequently he had a much better parent-reported quality of life. However, further dose escalations to 8mg led to aggressive behaviour and the dose was reduced to 6mg and then 4mg.

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Perampanel pharmacokinetics and combination therapy with perampanel

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Conflicts of interest:
Professor Patsalos has received, during the past 2 years, speaker or consultancy fees and/or research grants from Eisai, Sanofi Aventis and UCB Pharma.

The pharmacokinetic characteristics of a drug critically determines its therapeutics in terms of dosing frequency and therefore influences patient compliance, rate of dose titration and time course of achieving an optimum therapeutic response. Additionally, for newly licensed AEDs, knowledge of their propensity to interact with concomitant drugs is important because all AEDs are initially licensed for adjunctive therapy.[1,2] These considerations can make a difference as to whether therapy will be successful or will fail.

Perampanel pharmacokinetic characteristics:

Absorption and distribution:
After oral ingestion perampanel is rapidly absorbed (T_{max}, 0.25-2.0 hours) with a bioavailability of ~100% and is not subject to any significant first-pass metabolism. Its volume of distribution in adults is 1.1 L/kg and plasma protein binding, primarily to albumin, is ~95%. Food co-ingestion does not affect the extent of absorption, but C_{max} values are decreased by 40% and T_{max} is delayed by 2 hours. Perampanel demonstrates linear pharmacokinetics in healthy individuals at doses of 2-12mg and steady state is achieved within 14 days.[3-6]

Metabolism:
Perampanel is extensively metabolised (98%) in the liver, primarily by CYP3A4 (although CYP3A5 may also contribute)-mediated oxidation followed by sequential glucuronidation; the major metabolites being hydroxylated perampanel and various glucuronide conjugates.[3-6]

Elimination:
The mean plasma half-life of single-dose perampanel in adult healthy volunteers is 105 hours (range 52-129 hours). After multiple-dose administration, the plasma half-life of perampanel ranges 66-90 hours. In the presence of enzyme-inducing AEDs (e.g. carbamazepine) perampanel half-life values can decrease to ~25 hours. Seventy percent of a perampanel dose is excreted in faeces and only ~2% of an administered dose is excreted as unchanged perampanel in urine.[3-6]

Drug interaction profile:
In vitro, at clinically relevant concentrations, perampanel is neither a potent inhibitor nor an inducer of cytochrome P450 (CYP) isoenzymes or uridine diphosphate-glucuronosyltransferases (UGTs) and thus perampanel is not expected to cause pharmacokinetic interactions. However, because perampanel undergoes metabolism primarily via CYP3A4, an isoenzyme that is readily inducible and inhibitable, it will be the target of drugs that affect this isoenzyme.[3-6] Table 1 summarises the impact of perampanel on other drugs and vice versa.

Posology:
Perampanel is available as a tablet formulation (2, 4, 6, 8, 10 and 12mg) and its pharmacokinetics has important implications for its use. That perampanel exhibits linear pharmacokinetics and steady-state plasma concentrations are achieved within 14 days means that dosing strategies can be simple and, for any specific dose, optimum therapeutic response can be expected relatively quickly. Perampanel can be prescribed as a once-daily AED, due to its long half-life, with or without

Table 1

Drug interaction	Managing interaction
Cytochrome P450 inducers: Concomitant AEDs that are CYP3A4 inducers (carbamazepine, oxcarbazepine, phenytoin and topiramate) will increase perampanel clearance and reduce perampanel plasma concentrations.	Perampanel should be dosed to clinical effect. Avoid the use of strong CYP3A4 inducers other than AEDs (e.g. rifampin, St. John's wort).
Combined oral contraceptives (COCs): Perampanel at the 12mg once-daily dose decreases the effectiveness of COCs containing levonorgestrel.	Perampanel does not interact with the COC when dosed at 8mg or below. However, additional non-hormonal methods are recommended for doses above 8 mg.
AEDs not having any effect on perampanel concentration: clobazam, clonazepam, lamotrigine, levetiracetam, phenobarbital, primidone, valproic acid and zonisamide.	

Case study 5

A 64-year-old man experienced his first seizure aged 20 years. An EEG showed right temporal inter-ictal and ictal abnormalities, an MRI showed right temporal focal atrophy and the PET was normal. The patient had reduced verbal memory ability with significant visual memory impairment. He was first seen in 2002 when he was experiencing frequent daily complex partial seizures and secondarily generalised tonic–clonic seizures (2 to 3 per month) despite prior treatment with multiple AEDs. Levetiracetam 1500mg BD had been started in 2001: the secondarily generalised tonic-clonic seizures stopped but he continued to have ongoing daily complex partial seizures. The patient underwent right temporal lobectomy in 2004, which only provided brief initial benefit. Vagal nerve stimulation therapy was discussed and declined as was further resective surgery. Between 2002 and 2012 he failed multiple AEDs, including newer drugs (lacosamide and eslicarbazepine acetate).

Perampanel was initiated in December 2012 increasing by 2mg every 2 weeks to a maintenance dose of 8mg: concomitant medications included levetiracetam 1.5g twice daily, zonisamide 100mg twice daily, carbamazepine 200mg mane and 400mg nocte. In the four months to May 2013, the patient had experienced 16-20 seizure-free days per month with reduced complex partial seizures and no tonic–clonic seizures. In May 2013, the dose of perampanel was increased to 10mg daily and the patient complained of new dizziness; the plan is to reduce the dose of carbamazepine to 200mg twice daily over two weeks, with a view to weaning carbamazepine entirely over the next few months.

food, which simplifies prescribing and also can enhance patient compliance. When perampanel is added to an AED regimen comprising of a CYP3A4 inducer (e.g. carbamazepine, oxcarbazepine, phenytoin, topiramate), the associated decrease in perampanel half-life values[3] can be used to clinical advantage because, for any given perampanel dose, steady state concentrations will occur sooner and thus patients can be titrated faster and attain an optimum therapeutic response sooner. In this setting perampanel is dose titrated to clinical effect. However, if a patient is already on a dose of perampanel whereby a CYP3A4 inducing drug is co-prescribed, it will be necessary to increase the perampanel dose in order to maintain the anti-seizure effect of perampanel.

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Summary and Conclusions

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Conflicts of interest:

Dr Leach has received speakers' honoraria and honoraria for attending advisory boards for Eisai, GlaxoSmithKline, UCB and Janssen-Cilag. He supervises a clinical epilepsy fellow funded by an unrestricted grant from UCB.

Why perampanel?

Perampanel has been granted a European licence for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older[1] and early experience with the drug has been very positive. But what is it about perampanel that makes it a practical and effective AED?

The rationale for use of perampanel is compelling. Perampanel has a novel mode of action, being the only licensed anticonvulsant with proven effect in selectively blocking AMPA receptors, so reducing the excitatory effects of glutamate. This would explain its action in preventing seizures, and may explain its effect in patients unresponsive to previous AEDs. The half-life of perampanel is long, which allows for once-daily dosing, whether or not the drug is used alongside enzyme-inducing AEDs. Some patients find that single daily dosing improves adherence and reduces the impact of the drug regime on their daily life. Single daily dosing and a range of tablet denominations mean that titration is simple, and dosing at bedtime minimises the potential impact of dizziness as a side effect.

The effectiveness of perampanel for both partial and secondarily generalised seizures has been consistently demonstrated across the key clinical trials.[2] Perampanel was well tolerated in the trial population with the majority of TEAEs being mild to moderate in intensity; it is anticipated that the incidence of adverse effects may decrease with reducing speeds of titration.

Early experience of perampanel

In this supplement we have included case studies detailing real-life clinical experiences of perampanel in its first year since launch in the UK. The case studies

show the effectiveness of perampanel in a wide range of patients, including paediatric patients ≥ 12 years, elderly patients, patients with learning difficulties and patients with prior behavioural issues. The case studies also illustrate the effectiveness of perampanel in both complex partial seizures and secondarily generalised seizures, the impact of perampanel in improving patients' quality of life, and practical approaches to managing side effects with perampanel. Further data is expected soon, including long-term data from the 307 open-label extension study.[3,4]

The early experience of perampanel in the UK mirrors the experience of prescribers in other European countries: Professor Steinhoff and his team in Germany have detailed their early experience of perampanel in 45 patients (Box opposite).[5] In this group, 31.1% had a reduction in seizure frequency of at least 50% and almost 1 patient in 5 was free of seizures during the follow-up period. It is particularly notable that after 6 months the retention rate in this group was 71.1% (32/45 patients).

A UK multi-centre retrospective audit of patient experiences in using perampanel will provide further real-world insight on the benefits and risks of using this AED.[6] The audit will run for 18 months and collate demographic, neuro-epilepsy, efficacy and tolerability data; a sub-group of patients will be sent a questionnaire to assess quality of life and cognitive sequelae since the start of perampanel treatment. Preliminary approval has been obtained from approximately 40 centres to take part in the audit, with initial results expected in 2014.

Experience of perampanel use in Germany

A report of real-life clinical practice experiences in the year since launch of perampanel in Europe has been provided by Professor Steinhoff and colleagues at the Kehl-Kork Epilepsy Centre who have looked at responses to adjunctive perampanel for the patients who had ≥ 6 months of follow-up on perampanel (cut-off for inclusion within the analysis was 01 April 2013).[5] Demographic data for the cohort of 45 patients are listed below:

Gender:
24 female, 21 male

Mean age:
36 years (range 15 – 71 years)

Number of baseline AEDs:
1 (5; 11.1%), 2 (21; 46.7%), 3 (14; 31.1%), 4 (5, 11.1%)

Among this group, 31.1% (14/45) had a reduction in seizure frequency of ≥ 50% and 15.6% (7/45) were seizure free during the follow-up period. The perampanel mean dose in responders and seizure-free patients was 9.5mg. Adverse events were noted in 28 (62.2%) of the 45 patients, of which somnolence was the most common (occurring in 23 patients; 51.1%). Within the overall group, 29% (13/45) discontinued perampanel; seven due to lack of efficacy, five due to tolerability, and one due to concern about using the drug during an imminently planned pregnancy. After 6 months, 71.1% (32/45) of patients remained on treatment, thus the long-term retention rate for perampanel was comparable to those with other new AEDs.

Considerations for the future

It is easy to be blasé about the introduction of new AEDs. However, for many patients, epilepsy remains resistant to the currently available drug treatments. We owe it to our patients to remember the impact of uncontrolled epilepsy on their lives. We should not give up on these patients but instead strive to offer them hope.

As with other AEDs, initial experience with perampanel will determine how early in the treatment pathway it is used. As we develop our own modes and pace of dose titration, and get used to patterns of adverse effects in different populations, we will hopefully be able to develop our own ways of working with perampanel. In the coming years, we may be able to use perampanel in increasing numbers of patients for a wider spectrum of epilepsies and at an earlier stage in the pathway and this real-world experience will provide further insights on the usefulness of perampanel.

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PRESCRIBING INFORMATION

Fycompa®▼ (perampanel)

Please refer to the SPC before prescribing.

Presentation: Film-coated tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg perampanel. ***Indication:*** Adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older. ***Dose and administration: Adults and Adolescents:*** Starting dose is 2 mg daily. Dose should be titrated based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of between 4mg/day to 12mg/day. Dose should be taken orally once daily before bedtime. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel should be titrated no more frequently than at 1-week intervals. Withdraw gradually. ***Elderly and patients with renal or hepatic impairment:*** Dosage adjustments not required in elderly patients. Dosage adjustments not required in mild renal impairment, not recommended in patients with moderate or severe renal impairment or patients undergoing haemodialysis. Caution in mild or moderate hepatic impairment, titration should not be faster than every 2 weeks and maximum daily dosage not exceeding 8mg. Not recommended in severe hepatic impairment. ***Children and adolescents under 12 years:*** No data available. ***Contra-Indications:*** Hypersensitivity to perampanel or any excipient. ***Pregnancy:*** Not recommended. ***Lactation:*** Unknown if excreted into breast milk. A decision whether to discontinue breastfeeding or to discontinue/abstain from Fycompa therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. ***Warnings and Precautions:*** Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. At doses of 12 mg/day Fycompa may decrease the effectiveness of progestative-containing hormonal contraceptives. There appears to be an increased risk of falls, particularly in the elderly. Cases of aggression have been reported and dose titration should be followed; a dose reduction should be considered in case of persistence of aggressive symptoms. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse. Patients should be closely monitored for tolerability and clinical response when adding or removing cytochrome P450 inducers or inhibitors, or switching from concomitant non-inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly. There are no data regarding the effects of withdrawal of concomitant anti-epileptic medicinal products to achieve monotherapy with perampanel. Fycompa contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. ***Drug Interactions:*** The possibility of decreased efficacy of progestative-containing oral contraceptives should be considered for women needing Fycompa 12 mg/day and an additional reliable method (intra-uterine device (IUD), condom) is to be used. Carbamazepine, phenytoin, oxcarbazepine and topiramate have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. Fycompa did not affect in a clinically relevant manner the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid. The effect of perampanel on monohydroxycarbazepine concentrations is not known. Fycompa (6 mg once daily for 20 days) decreased midazolam AUC by 13% in healthy subjects. Strong inducers of cytochrome P450 such as rifampicin and hypericum are expected to decrease perampanel concentrations. Felbamate has been shown to decrease the concentrations of some drugs and may also reduce perampanel concentrations. Ketoconazole, a CYP3A4 inhibitor, increased perampanel AUC by 20% and prolonged perampanel half-life by 15%. Strong inhibitors of other cytochrome P450 isoforms could potentially also increase perampanel concentrations. Fycompa used in combination with other central nervous system (CNS) depressants such as alcohol can increase levels of anger, confusion, and depression. The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol. ***Side effects:*** Adverse reactions most commonly lead to discontinuation of perampanel were dizziness and somnolence. Refer to SPC for all side effects. Very common effects (≥ 1/10): dizziness, somnolence. Common effects (≥ 1/100, <1/10: decreased appetite, increased appetite, aggression, anger, anxiety, confusional state, ataxia, dysathria, balance disorder, irritability, diplopia, vision blurred, vertigo, nausea, back pain, gait disturbance, fatigue, weight increased, falls. Based on the clinical trial database of 143 adolescents, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults. ***Legal Category:*** POM ***Basic UK NHS cost:*** Fycompa 2 mg: packs of 7 £35.00, Fycompa 4 mg: packs of 28 £140.00, Fycompa 6 mg: packs of 28 £140.00, Fycompa 8 mg: packs of 28 £140.00, Fycompa 10 mg: packs of 28 £140.00, Fycompa 12 mg: packs of 28 £140.00 ***Marketing authorisation numbers:*** Fycompa 2 mg 7 tablets: EU/1/12/776/001, Fycompa 4 mg 28 tablets: EU/1/12/776/003, Fycompa 6 mg 28 tablets: EU/1/12/776/006, Fycompa 8 mg 28 tablets: EU/1/12/776/009, Fycompa 10mg 28 tablets: EU/1/12/776/012, Fycompa 12 mg 28 tablets: EU/1/12/776/015. Marketing authorisation holder: Eisai Ltd. ***Further Information from/Marketed by:*** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN ***Date of preparation:*** August 2012

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or EUmedinfo@eisai.net

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