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A retrospective, multicentre study of perampanel given as monotherapy in routine clinical care in people with epilepsy

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ABSTRACT

Purpose: Perampanel is approved for adjunctive treatment of focal seizures, with or without secondarily generalised seizures, and for primary generalised tonic-clonic seizures in people with epilepsy aged ≥12 years. Perampanel was recently approved for monotherapy use for partial seizures in the United States. This study provides insight into the feasibility of perampanel monotherapy in real-world settings.
Methods: This retrospective, non-interventional, multicentre study (NCT02736162) was conducted between January 2013 and March 2016 in specialist epilepsy centres in Europe and Russia. Eligible individuals had a diagnosis of epilepsy and received perampanel primary or secondary monotherapy as routine clinical care. The primary endpoint was proportion of individuals remaining on perampanel monotherapy, after conversion from perampanel adjunctive treatment, at 3, 6, 12, 18 and 24 months (retention rate).
Results: Sixty individuals were in the safety set (female, 63%; white, 97%; aged 18 to <65 years, 73%). Most (85%) received secondary monotherapy with perampanel. At study cut-off, 68% of individuals were continuing on perampanel monotherapy (secondary monotherapy: 55%). The median duration of retention was not calculable due to the high number of individuals ongoing on monotherapy. Twelve individuals had treatment-emergent adverse events that started during perampanel monotherapy, the most frequent was dizziness (5%). One serious treatment-emergent adverse event was reported (pneumonia during adjunctive perampanel treatment).
Conclusions: In this small retrospective study of individuals who received perampanel monotherapy, the majority maintained monotherapy. Perampanel monotherapy may be an achievable option in some people with epilepsy.

1. Introduction

Perampanel, a selective, non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, is approved for adjunctive treatment of focal seizures with or without secondarily generalised seizures and for primary generalised tonic-clonic seizures in people with epilepsy aged ≥12 years [1,2]. Perampanel was recently approved for monotherapy use for focal seizures in the United States. Approval of perampanel as an adjunctive treatment was based on Phase III clinical trial data in adjunctive settings [3–6] and reflects the usual

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EIAED, enzyme-inducing antiepileptic drug; IGE, idiopathic generalised epilepsy; ILAE, International League Against Epilepsy; TEAE, treatment-emergent adverse event.

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initial indication for antiepileptic drugs (AEDs). Specific labelling of AEDs as adjunctive treatments is, however, unique among central nervous system drugs and can restrict on-label use to polytherapy settings, which has been associated with increased toxicity, non-compliance and cost [7,8]. Due to these restrictions and ethical concerns around the use of placebo-controlled trials for AED monotherapy [7,9], open-label trials and specific epilepsy syndrome indications have been recommended to support monotherapy use [7].

Perampanel monotherapy has shown anti-seizure effects in several animal models of epilepsy and status epilepticus [10,11] but there have been no controlled trials of perampanel monotherapy in humans. Real-world evidence may be a useful approach to explore the feasibility of AED monotherapy in the clinic. We report the results of a retrospective study evaluating perampanel monotherapy in the routine clinical care of people with epilepsy.

2. Methods

2.1. Study design and population

This was a retrospective, non-interventional, multicentre study to investigate the dosage, efficacy and safety of perampanel given as monotherapy in routine clinical care to individuals with epilepsy (Eisai Inc. protocol E2007-G000-504; ClinicalTrials.gov identifier: NCT02736162). Data were collected retrospectively for individuals with epilepsy who received perampanel as primary or secondary (conversion) monotherapy between 1 January 2013 and 1 March 2016 at specialist epilepsy centres across Austria, Denmark, Germany, Russia, Spain and the United Kingdom (i.e., countries where perampanel was commercially available and being prescribed). Primary monotherapy was defined as the administration of perampanel in the absence of any concomitant AEDs, and secondary (conversion) monotherapy was defined as the conversion of perampanel from adjunctive therapy to monotherapy by withdrawing concomitant AEDs. Those defined as being on primary monotherapy may have previously taken other AEDs but would have permanently discontinued these prior to starting perampanel monotherapy (e.g. due to being in remission or subject choice), although this information was not specifically captured as part of this study.

Cases were identified by centres from electronic/paper medical and pharmacy records of individuals who were attending their usual epilepsy clinic and were prescribed perampanel as monotherapy based on the treating clinician's recommendation.

Given that this was a non-interventional study, the risk to participants in the study was limited to the possibility of a breach in their confidentiality with regard to personal identifiers or health information. Anonymised information was collected from medical records without any involvement or participation of individuals, and the sponsor had no access to individual medical records. Where applicable, Independent Ethics Committee and regulatory authority review and approval were obtained in accordance with local legislation.

2.2. Data collection

Each centre was responsible for its own data collection and reporting; available data were entered by centres into paper case report forms.

Where available, data on AED history, seizure frequency and safety were collected. Data for evaluation of seizure outcomes were obtained from medical records or seizure diaries, where available; if not available, investigator assessment of the therapeutic response was used.

Written informed consent must have been provided by each individual, or their legally authorised representative, for the use of the medical records, as per local requirements.

2.3. Objectives and analyses

All individuals who had received at least 1 dose of perampanel were included in the safety set and all individuals who had received perampanel and had seizure frequency data available (including data at pre-perampanel baseline) were included in the full analysis set.

The primary objective of the study was to assess the retention rate of perampanel when given as secondary monotherapy in routine clinical care. Accordingly, the proportions of individuals remaining on perampanel monotherapy (retention rates) at 3, 6, 12, 18 and 24 months were evaluated as primary endpoints, with an additional analysis at the study cut-off date of 1 March 2016. The denominators for these retention rates were the numbers of individuals who could have been exposed for each period of time. Retention rates were assessed in the safety set for a population of individuals who specifically received secondary monotherapy, and additional analyses included all individuals receiving primary or secondary monotherapy.

The following secondary endpoints, relating to changes in seizure frequency, were assessed in the full analysis set: the proportion of individuals who were seizure free for at least 3 months while receiving perampanel monotherapy; and changes in seizure frequency between pre-perampanel baseline (up to 3 months prior to the initiation of perampanel) and (1) the last 3 months of perampanel adjunctive treatment (only determined for individuals who received secondary monotherapy), (2) the first 3 months of perampanel monotherapy and (3) the last 3 months of perampanel monotherapy before the last follow-up (only determined for individuals with a minimum of 6 months of follow-up). Specifically, changes in seizure frequency were assessed as the following: median percent change in seizure frequency per 28 days; proportions of individuals with a reduction in seizure frequency of 50% (50% responder rate); and proportions of individuals with no change or a worsening of seizure frequency, based on qualitative clinical impression (i.e., investigator response of "stable/no change" or "worsened") or seizure frequency (i.e., no change or an increase in seizure frequency). Seizure-freedom rates were also assessed at the same 3 time periods; individuals with a seizure-free status recorded as unknown were included as not seizure free.

Maximum and median doses of perampanel during adjunctive treatment and monotherapy were recorded. Other safety endpoints included treatment-emergent adverse events (TEAEs) and serious TEAEs, assessed in the safety set from the initiation of perampanel monotherapy until 30 days after the last dose of perampanel monotherapy.

Other post hoc analyses explored the impact of prior AED use (including the use of enzyme-inducing AEDs [EIAEDs]) and epilepsy history. These analyses are described in more detail in Supplementary Methods A.1 in Appendix A.

3. Results

3.1. Study population and AED exposure

Data collection was started on 19 April 2016 and the last data items were collected on 14 July 2016. Of 1225 individuals prescribed perampanel across the centres, 69 (6%) were prescribed perampanel as monotherapy. Data were provided for 60 individuals (from 19 centres) who were included in the safety set; most had received perampanel as secondary monotherapy (n = 51; 85%)