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ADIS DRUG PROFILE

Perampanel

As Adjunctive Therapy in Patients with Partial-Onset Seizures

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Abstract Perampanel is a novel antiepileptic drug (AED) used as adjunctive therapy in adolescents and adults with partial-onset seizures (with or without secondarily generalized seizures). It is a selective, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors on post-synaptic neurons, and is the first in this new class of AED known as AMPA receptor antagonists. In three randomized, double-blind, placebo-controlled, phase III trials in adolescent and adult patients with refractory partial-onset seizures, once-daily administration of perampanel 4, 8 and 12 mg/day (6-week titration phase followed by 13-week maintenance phase), as adjunctive therapy with one to three AEDs, was statistically superior to adjunctive placebo in achieving the key efficacy endpoints of the median percentage change from baseline in seizure frequency and/or the proportion of patients with a ≥50 % reduction in seizure frequency relative to baseline. Adverse events were usually mild or moderate in severity and the most frequent treatment-emergent events reported among perampanel recipients were CNS-related, such as dizziness, somnolence, headache and fatigue. Interim data from a large extension study (16-week blinded conversion period followed by open-label maintenance phase), which enrolled patients who completed the phase III trials, showed a similar group response for the reduction in seizure frequency over at least 1 year of adjunctive treatment with perampanel. Perampanel was

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Key features and properties of perampanel (Fycompa®)

Indication

Adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged ≥12 years

Mechanism of action

Selective, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors

Dosage and administration

Route of administration	Oral
Administration schedule	Once daily at bedtime
Effective dosage range	4–12 mg/day (also see local prescribing information)
Initiation of therapy	2 mg/day
Gradual upward titration	By increments of 2 mg/day (at 2-week intervals in the EU and 1-week intervals in the USA)
If patient receiving carbamazepine or other enzyme inducer	See local prescribing information

Pharmacokinetic properties

Absorption	Readily absorbed (food delays rate but not extent of absorption)
Distribution	Volume of distribution not reported; ≈95 % bound to plasma proteins
Metabolism	Extensively metabolized by cytochrome P450 (CYP) 3A4 and/or 3A5 (and possibly other pathways) with subsequent glucuronidation
Elimination	30 % urine, 70 % faeces (primarily as metabolites); half-life ≈105 h (reduced to ≈25 h with concurrent carbamazepine)

Most commonly reported adverse events

Dizziness, somnolence, headache, fatigue

generally well tolerated over the longer-term in extension studies, with no unexpected adverse events reported. On the basis of its overall clinical profile and unique mechanism of action, perampanel is a useful adjunctive treatment option in patients with refractory partial-onset seizures.

1 Introduction

Epilepsy is the most common of all neurological conditions and affects more than 50 million people worldwide, or about 1 % of the population [1, 2]. Partial seizures, also known as focal seizures because they originate in only part of the brain, are more common than generalized seizures, especially in adult-onset epilepsy [1, 2]. In industrialized countries, partial seizures occur in ≈60 % of individuals with epilepsy [1]. They can be categorized as either simple partial seizures, which are not associated with loss of consciousness, or complex partial seizures, which result in altered or loss of consciousness [3, 4]. In some cases, partial-onset seizures can become secondarily generalized, such that epileptic activity spreads to both hemispheres of the brain, resulting in loss of consciousness and often tonic-clonic seizures [4].

A wide range of antiepileptic drugs (AEDs) is available to control seizures in patients with epilepsy [5, 6], although about one-quarter to one-third of patients will continue to have seizures despite receiving adequate trials of AEDs alone or in combination [7, 8]. Moreover, epilepsy in general and refractory epilepsy in particular, is associated with increased mortality and morbidity, as well as reduced quality of life [2, 7, 9]. The need for AEDs with improved efficacy and favourable tolerability profiles has led to the development of a number of new AEDs in recent years, many of which are used as adjunctive treatment of partial-onset seizures [5, 6]. One such agent, and the first in its class, is perampanel (Fycompa®) [Fig. 1], which is a selective, noncompetitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors. Perampanel was recently approved in the EU and in the USA as adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This article reviews the pharmacological properties, clinical efficacy and tolerability profile of perampanel as adjunctive therapy in the management of partial-onset seizures.

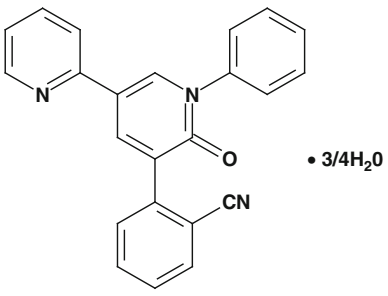

Fig. 1 Chemical structure of perampanel (3/4 hydrate), which has a configuration of three molecules of perampanel to four molecules of water

Data Selection

Sources: Medical literature (including published and unpublished data) on 'perampanel' was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were 'perampanel' and ('epilepsy' or 'partial seizures' or 'focal seizures' or 'partial-onset seizures'). Searches were last updated 31 October 2012.

Selection: Studies in patients with partial-onset seizures who received perampanel as adjunctive treatment. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Perampanel, partial-onset seizures, epilepsy, pharmacodynamics, pharmacokinetics, drug interactions, therapeutic use, tolerability.

2 Pharmacodynamic Profile

Perampanel is a selective, noncompetitive antagonist of ionotropic AMPA-type glutamate receptors on post-synaptic neurons, and is the first in this new class of AED known as AMPA receptor antagonists or AMPA-type glutamate receptor antagonists [10, 11]. AMPA receptors are ligand-gated ion channels activated by glutamate, the major excitatory neurotransmitter in the CNS, which is thought to have an important role in inducing seizures [12–14]. Although there are other ionotropic glutamate receptors in the CNS (*N*-methyl-D-aspartate [NMDA], kainate), AMPA receptors appear to be the predominant mediator of excitatory neurotransmission and are involved in the generation and spread of seizure activity [14–16].

In vitro studies have provided evidence that perampanel is a noncompetitive and selective AMPA receptor antagonist [10, 11, 17]. AMPA-induced increases in intracellular free calcium ion concentration ($[Ca^{2+}]_i$) were inhibited by perampanel in a concentration-dependent manner in rat cortical neurons, with a 50 % inhibitory concentration (IC_{50}) of 93 nmol/L [11]. This IC_{50} value for perampanel was >100-fold lower than that for GYKI52466, a well characterized noncompetitive AMPA receptor antagonist.

In contrast, perampanel had little or no inhibitory effect on NMDA-induced increases in $[Ca^{2+}]_i$ [11]. The selectivity of perampanel for AMPA receptors in synaptic transmission was demonstrated in vitro using rat hippocampal slices [17]. In this study, perampanel reduced synaptic responses mediated by AMPA receptors, but not those mediated by NMDA or kainate receptors [17]. In rat forebrain membranes, perampanel did not compete with AMPA for binding to the AMPA receptor, but perampanel binding was displaced by GYK152466 and by another noncompetitive AMPA receptor antagonist, thus showing that perampanel acts as an allosteric or noncompetitive antagonist at AMPA receptors [11].

Preclinical studies in murine models of epilepsy have demonstrated the anticonvulsant activity of perampanel [11]. Perampanel protected mice from maximal electroshock-, pentylenetetrazole- or 6 Hz-induced seizures, with 50 % effective dose (ED_{50}) values that were markedly lower than those for carbamazepine or valproate [11]. In amygdala-kindled rats, motor seizure duration and afterdischarge duration were significantly reduced and afterdischarge threshold was significantly increased by perampanel compared with vehicle [11].

3 Pharmacokinetic Profile

Perampanel is orally administered and has a linear pharmacokinetic profile [10, 18] that can be described by a one-compartment model with first-order elimination [19]. The pharmacokinetic profile of perampanel is characterized by rapid absorption following oral administration, extensive metabolism and slow elimination, although the clearance of perampanel can be markedly increased with concurrent administration of strong inducers of cytochrome P450 (CYP) 3A isoenzymes (e.g. carbamazepine) [10]. Published data on the pharmacokinetics of perampanel are limited to the EU Summary of Product Characteristics (SmPC) [10], the US prescribing information [20] and various conference abstract reports or posters [18, 19, 21, 22].

3.1 Absorption and Distribution

Following oral administration, perampanel is readily absorbed (bioavailability not reported) [10], with peak plasma concentrations (C_{max}) achieved in ≈1 h [21]. Food does not affect the extent of absorption, but can delay C_{max} by 2 h compared with administration in a fasted state [10]. Population pharmacokinetic modelling using data from phase III clinical trials in patients with partial-onset seizures who received once-daily perampanel as adjunctive therapy with other AEDs showed that the mean plasma perampanel concentrations were ≈400 nmol/L with perampanel 4 mg/day and ≈1000 nmol/L with perampanel 12 mg/day [17, 22]. Further analysis of clinical and pharmacokinetic data from the phase III studies showed that log-transformed seizure frequency decreased linearly with increasing average plasma perampanel concentrations at steady state [18].

The volume of distribution of perampanel has not been reported. In vitro studies indicate that perampanel is ≈95 % bound to plasma proteins [10]. Perampanel does not appear to be a substrate for (or significant inhibitor of) organic anion transporting polypeptides, organic anion transporters, organic cation transporters or the efflux transporter P-glycoprotein [10].

3.2 Metabolism and Elimination

Perampanel is extensively metabolized by primary oxidation and subsequent glucuronidation [10]. The metabolic fate of perampanel has not been fully elucidated, but available data from in vitro studies using recombinant human CYP enzymes and human liver microsomes indicate that oxidative metabolism of the drug is mediated by CYP3A4 and/or CYP3A5 isoenzymes (and possibly other pathways) [10, 20].

Following single-dose administration of radiolabelled perampanel in healthy elderly volunteers, 30 % of the dose was recovered in the urine and 70 % in the faeces, primarily as oxidative and conjugated metabolites in both urine and faeces [10]. Only trace amounts of perampanel metabolites could be detected in plasma.

The average elimination half-life ($t_{½}$) of perampanel was 105 h in a pooled analysis of data from 19 phase I trials in healthy volunteers [10]. Other data from two phase I studies with perampanel indicate $t_{½}$ values ranging from 52 to 129 h after single-dose administration and from 66 to 90 h after multiple-dose administration for 14 days [21].

Clearance of perampanel was 17 % lower in females than in male patients (0.605 vs. 0.730 L/h) in a population pharmacokinetic analysis of patients with partial-onset seizures who participated in clinical trials [10, 22]. Neither age nor race had a significant effect on the pharmacokinetics of perampanel in a population pharmacokinetic analysis of data from patients aged 12–74 years in clinical trials [10, 22]. Although the pharmacokinetics of perampanel have not been formally evaluated in patients with renal impairment, the clearance of perampanel was not affected by creatinine clearance over a range of 39 to 160 mL/min in clinical trials [10]. The $t_{½}$ of perampanel was prolonged in patients with mildly impaired (Child-Pugh A) [306 vs. 125 h] or moderately impaired (Child-Pugh B) [295 vs. 139 h] hepatic function, compared with matched controls [10].

3.3 Drug Interactions

An overview of pharmacokinetic drug interactions with perampanel is presented in Table 1 [10, 19, 20, 22]. Since perampanel is approved for use as adjunctive therapy, clinically relevant pharmacokinetic drug interactions between perampanel and other AEDs are of particular interest. Most notable are interactions with AEDs that are known to induce CYP isoenzymes (e.g. CYP3A4) [10, 19]. For example, the $t_{½}$ of perampanel was reduced to ≈25 h when perampanel and carbamazepine were used concurrently in clinical trials [10]. In a population pharmacokinetic analysis of data from patients with partial-onset seizures who participated in phase III clinical trials, the average steady-state plasma concentration of perampanel was decreased by 3-fold with concurrent carbamazepine and by 2-fold with either phenytoin or oxcarbazepine [10, 19, 22]. Perampanel did not have a clinically relevant effect on the plasma concentrations of these AEDs [10, 22]. There were also no clinically significant interactions between perampanel and a range of other AEDs that were used concurrently in clinical trials [10, 22]. Perampanel reduces the clearance of oxcarbazepine by 26 % and increases average steady-state plasma concentrations by 35 %, although the effect on the active metabolite of oxcarbazepine has not been evaluated [10]. Felbamate has been shown to reduce the plasma concentrations of some drugs and may have a similar effect on perampanel, although no formal pharmacokinetic analysis has been conducted [10].

Other strong inducers of CYP, such as rifampicin (rifampin) may be expected to reduce plasma concentrations of perampanel [10]. US prescribing information states that concomitant use of perampanel with other strong CYP3A inducers, such as rifampicin or St John's wort, should be avoided [20], although no specific recommendations are included in the EU SmPC [10]. Conversely, strong inhibitors of CYP could potentially increase plasma perampanel concentrations [10]. A pharmacokinetic study in healthy volunteers found that ketoconazole 400 mg/day for 10 days increased the area under the plasma concentration-time curve (AUC) of perampanel by 20 % and its $t_{½}$ by 15 % [10].

In women receiving a combined oral contraceptive, concurrent administration of perampanel 12 mg/day (but not 4 or 8 mg/day) for 3 weeks reduced the mean C_{max} and AUC values of levonorgestrel by 40 % [10]. The AUC of ethinylestradiol was unaffected, although there was a reduction in C_{max} by 18 %. In the EU, an additional form of birth control should be considered for women using progestogen-containing oral contraceptives who are also receiving perampanel at its highest recommended dosage level of 12 mg/day [10]. US recommendations are generally similar (see Table 1) [20].

Perampanel 6 mg/day for 20 days reduced the AUC of midazolam by 13 % when these drugs were coadministered, and it is possible that the effect could be greater with increased dosages of perampanel [10].

Perampanel may also be associated with pharmacodynamic interactions with CNS depressants, including alcohol, as concurrent use may increase CNS depression [10, 20]. In healthy volunteers, perampanel had an additive or supra-additive effect to that of alcohol on impairing driving ability or similar tasks involving alertness and vigilance [10, 20].

4 Therapeutic Efficacy

4.1 Randomized Phase III Trials

Three randomized, double-blind, placebo-controlled, phase III trials (Studies 304 [23], 305 [24] and 306 [25]) have been conducted with adjunctive perampanel for refractory partial-onset seizures. Dosage regimens evaluated in these multinational phase III studies were based on two phase II dose-escalation studies (Studies 206 and 208, and a population pharmacokinetic analysis from these studies), which provided preliminary evidence of efficacy and showed that perampanel was generally well tolerated across a dosage range of 2–12 mg/day [26].

The three phase III trials were of similar design and used the same inclusion and exclusion criteria [23–25]. Patients aged ≥12 years with a diagnosis of simple or complex partial-onset seizures, with or without secondary generalization, were eligible for enrolment. Patients had to have uncontrolled partial-onset seizures despite treatment with at least two different AEDs within the previous 2 years. During the 6-week baseline phase of the trials (prior to randomization), patients had to have at least five partial seizures and could not have a seizure-free period >25 days. Patients were also required to be receiving stable dosage regimens of one to three AEDs for ≥3 weeks prior to randomization. Clinically significant medical or psychiatric conditions and a history of non-epileptic or psychogenic seizures were among the exclusion criteria.

Patients meeting the seizure frequency inclusion criteria during the 6-week baseline phase of the trials were then randomized to receive once-daily adjunctive treatment with perampanel or placebo for 19 weeks, which included a 6-week titration period and a 13-week maintenance period [23–25]. In Study 304 [23] and Study 305 [24], patients were randomized in a 1:1:1 ratio to perampanel 8 or 12 mg/day or placebo. In Study 306 [25], patients were randomized in a 1:1:1:1 ratio to perampanel 2, 4 or 8 mg/day or placebo. During the titration phase of the trials, perampanel dosage was increased from 2 mg/day

Table 1 Overview of pharmacokinetic drug interactions with perampanel [10, 19, 20, 22]

Concurrently administered drug	Effect on average steady-state plasma perampanel concentration[a]	Effect on average steady-state plasma concentration of concurrently administered drug[a,b]	Clinical recommendation (if any)
Antiepileptic drugs			
Carbamazepine	3-fold reduction		More rapid (i.e. weekly) dosage titration of perampanel (EU) or higher starting dosage of perampanel (i.e. 4 mg/day) [USA]
Felbamate	May reduce, but no specific data		
Oxcarbazepine	2-fold reduction	35 % increase	As for carbamazepine
Phenytoin	2-fold reduction		As for carbamazepine
Topiramate	20 % reduction		
Other drugs			
Ketoconazole	20 % increase		
Levonorgestrel		40 % reduction (with highest recommended dosage of perampanel)	If taking perampanel 12 mg/day with progestogen-containing oral contraceptive (EU) or perampanel with levonorgestrel-containing oral or implant contraceptive (USA), use additional reliable method of birth control
Midazolam		13 % reduction (with perampanel 6 mg/day)	
Rifampicin (rifampin)	May reduce, but no specific data		Strong inducers of cytochrome P450 3A isoenzymes should be avoided (USA)
St John's wort	May reduce, but no specific data		As for rifampicin

AUC area under the plasma concentration-time curve, C_{max} peak plasma concentration

[a] Values in the table reflect average steady-state plasma concentrations, other than for ketoconazole (AUC), levonorgestrel (both AUC and mean C_{max}) and midazolam (AUC)

[b] In general, perampanel has little or no influence on the plasma concentrations of concurrently administered antiepileptic drugs other than oxcarbazepine (although the effect on the active metabolite monohydroxycarbazepine is unknown)

(by increments of 2 mg/day at weekly intervals) up to the target dosage [23–25]. After the maintenance period, patients could enter an extension study or discontinue study treatment; follow-up visits were conducted at 4 weeks after discontinuation of study treatment.

The key efficacy endpoints were based on seizure counts from patient diaries and included the following: (1) the percentage change from baseline to the end of the 19-week double-blind period in seizure frequency per 28 days; and (2) the proportion of patients with a ≥50 % reduction in seizure frequency in the 13-week maintenance period relative to baseline [23–25]. The 50 % responder rate was designated as the primary endpoint in the EU and the percentage change in seizure frequency was considered the primary endpoint in the USA. Efficacy analyses were based on the intent-to-treat (ITT) population and statistical analysis included a ranked analysis of covariance model.

In all three studies, baseline characteristics were similar across treatment groups [23–25]. The mean age range was ≈33–37 years, the mean time since epilepsy diagnosis was ≈17.5–24 years and the majority (80–93 %) of patients were receiving two or three other AEDs (most commonly including carbamazepine, lamotrigine, levetiracetam and/or valproate). The mean number of prior lifetime AEDs was not reported in any of the trials. Seizure frequency and type were evenly distributed between treatment groups in each study.

The main findings from the three phase III trials [23–25] with perampanel are presented in Table 2 and Fig. 2. When used as adjunctive therapy for refractory partial-onset seizures, perampanel 4–12 mg/day was statistically superior to adjunctive placebo in reducing the seizure frequency during the 19-week double-blind period and/or in terms of the 50 % responder rate during the 13-week double-blind maintenance period across the three studies [23–25]. In Studies 305 [24] and 306 [25], perampanel 4, 8 and 12 mg/day were statistically superior to placebo for both of these key endpoints, whereas in Study 304 [23] perampanel 8 and 12 mg/day were associated with significantly greater median percentage reductions in seizure frequency than placebo, but there were no statistically significant between-group differences for the 50 % responder rates

Table 2 Main findings of phase III trials with perampanel as adjunctive therapy in patients (aged ≥12 years) with partial-onset seizures

Reference	Regimen (mg/day)	No. of patients	Median BL seizure frequency per 28 days	Median % change from BL in seizure frequency over 19-week double-blind period[a]	50 % responder rate[b] over 13-week double-blind maintenance period[c]
Study 304 [23]	PER 8	133	14.3	−26.3*	37.6
	PER 12	133	12.0	−34.5*	36.1
	Placebo	121	13.7	−21.0	26.4
Study 305 [24]	PER 8	129	13.0	−30.5***	33.3**
	PER 12	121	13.7	−17.6*	33.9***
	Placebo	136	11.8	−9.7	14.7
Study 306 [25]	PER 2	180	10.1	−13.6	20.6
	PER 4	172	10.0	−23.3**	28.5*
	PER 8	169	10.9	−30.8***	34.9***
	Placebo	184	9.3	−10.7	17.9

BL baseline, *PER* perampanel

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. placebo

[a] A primary endpoint for the USA and a secondary endpoint for the EU

[b] Percentage of patients who experienced at least a 50 % reduction in seizure frequency

[c] A primary endpoint for the EU and a secondary endpoint for the USA

(see Table 2). Across the three studies, the median percentage change from baseline in seizure frequency over the 19-week double-blind period for perampanel 2, 4, 8 and 12 mg/day was 13.6, 23.3, 26.3–30.8 and 17.6–34.5 %, respectively, compared with 9.7–21.0 % for placebo. The 50 % responder rates over the 13-week double-blind maintenance period were 20.6, 28.5, 33.3–37.6 and 33.9–36.1 % for perampanel 2, 4, 8 and 12 mg/day compared with 14.7–26.4 % for placebo [23–25].

Study 306 [25] showed a positive dose response with perampanel 2–8 mg/day for the median percentage change in seizure frequency during the double-blind period ($p < 0.001$) and also confirmed that the minimal effective dosage of perampanel is 4 mg/day. Various pooled analyses of the phase III trials also examined the dose-response effect of perampanel (see Sect. 4.3). In addition, US prescribing information states that a dosage of 12 mg/day resulted in somewhat greater reductions in seizure rates than a dosage of 8 mg/day, but with a substantial increase in adverse events, and individual dosing should be adjusted based on clinical response and tolerability [20]. It is noteworthy, however, that increased efficacy with 12 mg/day compared with 8 mg/day was not a consistent finding of the two phase III trials (Studies 304 [23] and 305 [24]) that included these regimens.

An important secondary endpoint in all three trials was the median percentage change in the frequency of complex partial plus secondarily generalized seizures, which were reported by ≈65–75 % of patients at baseline [23–25]. In the double-blind phase of the three studies, adjunctive therapy with perampanel 4–12 mg/day had significantly greater efficacy on this measure than adjunctive placebo (see Fig. 3). In Study 304 [23], the frequency (per 28 days) was reduced from baseline by 33.0 and 33.1 % with perampanel 8 and 12 mg/day, respectively, compared with a reduction of 17.9 % with placebo ($p < 0.01$ for both vs. placebo). Corresponding results from Study 305 [24] were reductions of 32.7 % ($p < 0.001$ vs. placebo) and 21.9 % ($p = 0.005$ vs. placebo) with perampanel 8 and 12 mg/day compared with a reduction of 8.1 % with placebo. In Study 306 [25], both perampanel 4 and 8 mg/day were statistically superior to placebo, with the frequency of these seizures being reduced by 31.2 % ($p < 0.01$ vs. placebo), 38.7 % ($p < 0.001$ vs. placebo) and 17.6 % for the respective treatment groups.

A subanalysis of 50 % responder rates in Study 304 showed regional differences in the efficacy of perampanel [23]. For the North American cohort ($n = 227$), there were statistically significant differences between both perampanel 8 and 12 mg/day compared with placebo (40.5 and 40.0 vs. 21.9%; $p < 0.05$ for both comparisons). In contrast, the respective rates in Central and South America ($n = 160$) were 33.9 and 30.2 versus 33.3%, with no statistically significant between-group differences.

Across all three studies there was also a general trend for more perampanel than placebo recipients being assessed by investigators as "much" or "very much" improved at the end of the double-blind study period, as assessed by the Clinical Global Impression of Change (CGI-C) scale [23–25].

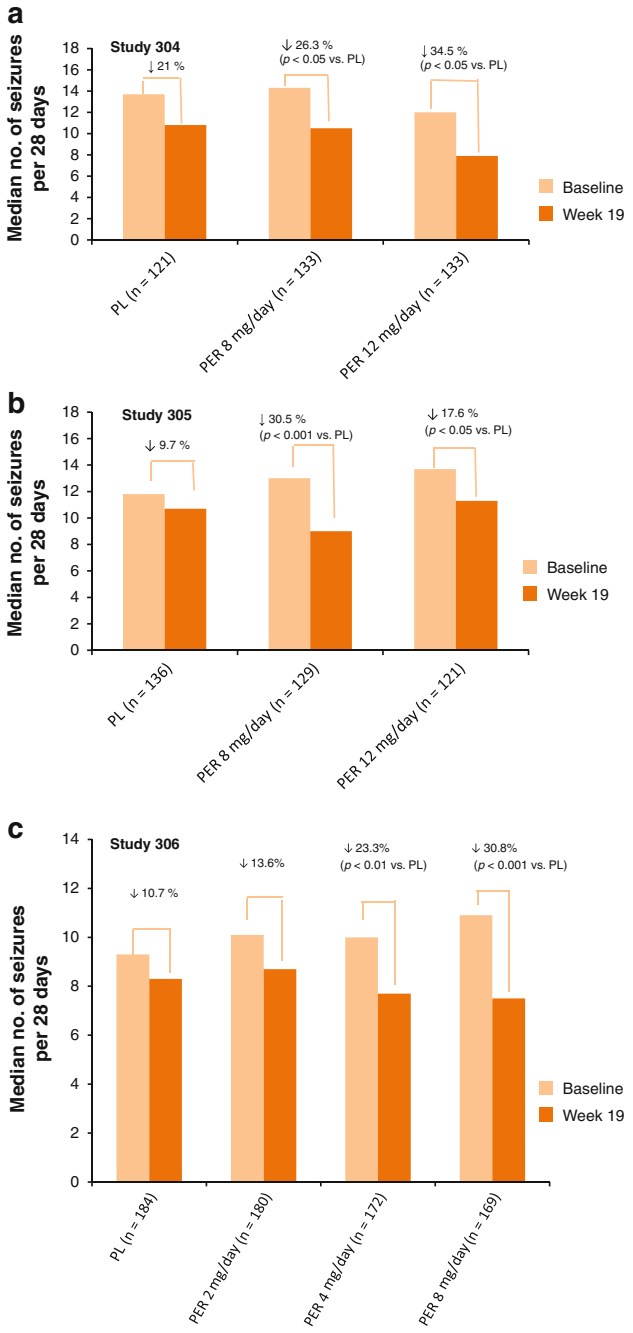

Fig. 2 Seizure frequency data from phase III trials with perampanel as adjunctive therapy in patients with refractory partial-onset seizures. Median number of seizures per 28 days at baseline and over the 19-week double-blind period in **a** Study 304 [23], **b** Study 305 [24] and **c** Study 306 [25]. *PER* perampanel, *PL* placebo

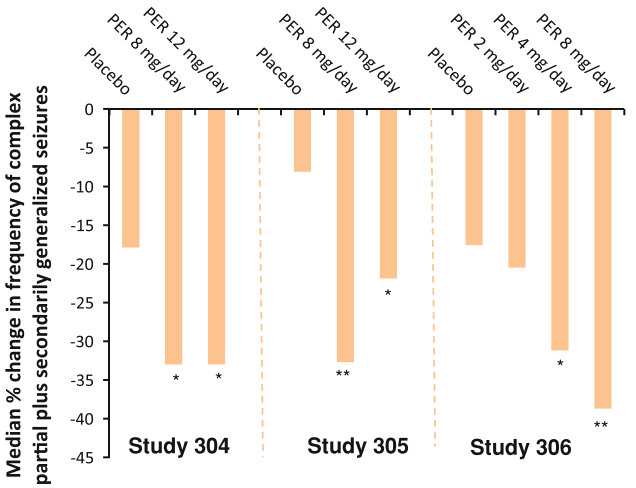

Fig. 3 Efficacy of adjunctive perampanel therapy on complex partial plus secondarily generalized seizures (a secondary endpoint) in phase III trials. Median percentage change in frequency of complex partial plus secondarily generalized seizures per 28 days at baseline and over the 19-week double-blind period in Studies 304 ($n = 279$) [23], 305 ($n = 262$) [24] and 306 ($n = 487$) [25]. *PER* perampanel; * $p < 0.01$, ** $p < 0.001$ vs. placebo

4.2 Extension of Phase III Trials

Patients completing the phase III studies (Sect. 4.1) could enter extension Study 307 [27], which included an initial 16-week blinded conversion period during which patients who had received placebo or perampanel <12 mg/day in the phase III trials had their perampanel dosage titrated upwards in increments of 2 mg/day every 2 weeks to the maximum tolerated dosage (up to 12 mg/day). Patients who had been receiving 12 mg/day in the phase III trials were maintained on this dosage. The on-going extension study includes a planned 256-week open-label maintenance period and a 4-week follow-up phase. Patients were maintained on the maximum tolerated dosage of perampanel if feasible, although dosage adjustments, discontinuation or change in concurrent AEDs were permitted, which may have contributed to maintain efficacy.

The primary objective of the extension study was to assess the long-term tolerability and safety of perampanel [27]. These data are summarized in Sect. 5 and showed a similar tolerability profile to that reported in shorter-term trials.

At a specified cut-off date for interim analysis, efficacy data were available for the ITT population of 1207 patients, which included 1006, 588 and 19 patients who received treatment with perampanel for ≥26 weeks, ≥1 year and ≥2 years, respectively [27]. The majority of patients (>90 %) received perampanel at dosages of 10 or 12 mg/day.

Compared with the pre-perampanel baseline period of the phase III trials, seizure frequency per 28 days was reduced by a median of ≈42 % at the end of the 16-week blinded conversion period, and there was no apparent difference between patients initially randomized to placebo (−42.4 %, $n = 369$) and those initially randomized to perampanel (−41.5 %, $n = 817$) [27]. The group response

for reduction in seizure frequency was similar during the open-label maintenance period. For example, among the 588 patients with at least 1 year of perampanel exposure, the median reduction in seizure frequency per 28 days during the last 13 weeks of exposure compared with the pre-perampanel baseline period was 47.2 %. The corresponding value for the small number of patients with at least 2 years' exposure was 56.0 %.

Similar results were reported for the 50 % responder rates. At the end of the blinded conversion period, the proportions of patients with a ≥50 % reduction in seizure frequency compared with baseline were 44.2 and 43.3 % for those initially randomized to placebo and perampanel, respectively [27]. Group responses for 50 % responder rates were also similar during the open-label maintenance period. However, the extension study did not examine loss of initial efficacy (i.e. development of tolerance) and patients were allowed to change their concomitant medication to maintain efficacy. The study authors also cited the lack of a placebo comparison in the maintenance phase as a limitation of the extension study [27].

4.3 Pooled and Subgroup Analyses

Results of various pooled or subgroup analyses of the phase III studies with perampanel have been reported, primarily as abstracts and posters. The most relevant and contributory data from these reports are included in this section. In particular, Table 3 includes the main findings from pooled analyses of Studies 304, 305 and 306 using actual (final) dosages of perampanel received by patients who completed the double-blind phase of the trials [28–30]. The analyses included patients from North America, Europe, Asia/Pacific region, South Africa and Australia, but excluded patients enrolled in Central and South America because of high placebo responses resulting in a significant treatment by region interaction outcome observed in these countries. The overall findings were generally similar to those of the individual trials. One analysis showed dose-dependent improvements in 50 and 75 % responder rates with perampanel 4–12 mg/day [29].

The efficacy of perampanel 12 mg/day was deemed to be slightly better than that of 8 mg/day (although statistical analysis was not reported), according to a pooled, actual-dose analysis of data from Study 304, Study 305 and the extension of the phase III trials [31]. The analysis included patients (excluding those from Central and South America) who completed the randomized phase of Studies 304 and 305 with perampanel 8 mg/day and whose last dose received during the conversion period of the open-label extension study was 12 mg/day. The median percentage change from baseline in seizure frequency per 28 days improved from −32.4 % with perampanel 8 mg/day to −43.4 % with perampanel 12 mg/day. Similar trends were noted for the 50 % responder rates (37.8 vs. 43.5 %) and improvements in the frequency of secondarily generalized seizures (−46 vs. −54 %).

Study 306 [25], which showed a positive dose response with perampanel 2–8 mg/day for the median percentage change from baseline in seizure frequency during the double-blind period ($p < 0.001$) [Sect. 4.1], also found a similar dose-response effect was maintained across

Table 3 Main findings from selected pooled analyses of the three phase III trials (Studies 304, 305 and 306) [reported as abstracts]

Study and parameter[a]	Placebo ($n = 348$)	PER 2 mg/day ($n = 161$)	PER 4 mg/day ($n = 159$)	PER 8 mg/day ($n = 287$)	PER 12 mg/day ($n = 114$)
Ben-Menachem et al. [28]					
Median % change in seizure frequency	−11.7	−17.3	−24.1	−31.9	−26.2
Krauss et al. [29]					
% of pts with ≥50 % reduction in seizure frequency	18.4	22.4	30.8	37.6	39.5
% of pts with ≥75 % reduction in seizure frequency	5.7	10.6	12.6	18.8	20.2
% of pts seizure free	1.1	1.9	5.0	3.8	4.4
Steinhoff et al. [30]					
Median % change in CPS + SGS frequency[b]	−14.6	−26.6	−35.6	−35.9	−30.3

CPS complex partial seizure, *PER* perampanel, *pts* patients, *SGS* secondarily generalized seizure

[a] Analyses included actual (last) dosages received by completers of the double-blind period of the trials and excluded data from patients enrolled in Central and South America because of high placebo responses observed in these centres. Comparisons were for seizure frequency per 28 days vs. baseline

[b] Patient numbers for this parameter were ≈90 % of those reported in the column headings, as follows: placebo ($n = 319$), PER 2 mg/day ($n = 150$), PER 4 mg/day ($n = 145$), PER 8 mg/day ($n = 267$), PER 12 mg/day ($n = 104$)

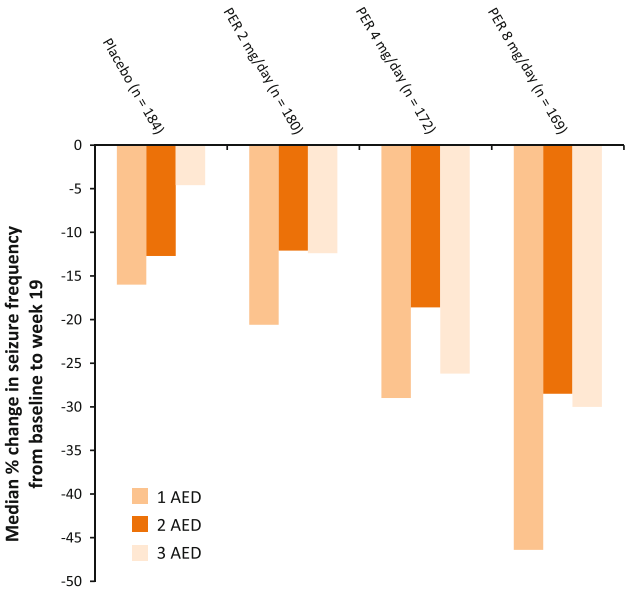

Fig. 4 Seizure frequency data from the phase III Study 306 [25] in subgroups of patients receiving one ($n = 19$–30 across treatment groups), two ($n = 80$–90) or three ($n = 60$–70) concurrent antiepileptic drugs. Approximately 85 % of patients were receiving two or three concurrent antiepileptic drugs across the treatment groups. *AED* antiepileptic drug

subgroups according to the number of other AEDs the patients were receiving (see Fig. 4). There was also a general trend for better results among the ≈15 % of patients receiving only one other AED, compared with two or three other AEDs, although this result is not unexpected.

Effects of perampanel adjunctive therapy in patients already taking each of the most common AEDs (carbamazepine, valproate, lamotrigine, levetiracetam and oxcarbazepine) have been studied in the pooled dataset [32]. Using actual-dose data from completers of the double-blind period of the phase III trials (excluding Central and South American centres), an increased benefit from increasing dosages of perampanel was observed over the range of 4–12 mg/day.

Another pooled analysis of data from the three phase III trials showed that perampanel 4–12 mg/day significantly ($p \leq 0.02$) prolonged the time to seizure recurrence compared with placebo [33], and a subgroup analysis of Study 306 found that the efficacy of perampanel 4 or 8 mg/day in adolescent patients ($n = 60$) was generally similar to that of the overall study population, although these findings require confirmation in a larger group of adolescents [34].

Baseline characteristics of patients enrolled in the registration trials for perampanel were compared with those for five other second- and third-generation AEDs in a recent abstract report, and results suggest that patients who participated in the perampanel trials may have been more difficult to treat (e.g. generally higher seizure frequency, more often had histories of secondarily generalized seizures, receiving more AEDs at baseline) [35].

5 Tolerability

According to the EU SmPC for perampanel [10], dizziness and somnolence are the most frequently reported adverse events (incidence ≥10 %) and the most common adverse events leading to discontinuation of perampanel (≥1 % of patients). Pooled data from the phase III clinical trials with perampanel in patients with refractory partial-onset seizures indicate that 1.7, 4.2 and 13.7 % of patients randomized to perampanel 4, 8 and 12 mg/day, respectively, discontinued treatment because of an adverse event [10].

In the individual phase III trials (Studies 304 [23], 305 [24] and 306 [25]), adverse events were largely mild or moderate in severity and the most frequently reported adverse events were dizziness and somnolence. There were no clinically important mean changes in laboratory values or ECG findings [23–25]. In particular, perampanel up to 12 mg/day did not prolong the corrected QT (QTc) interval and did not affect QRS duration [10]. The proportion of patients with a ≥7 % increase in body weight was generally higher among perampanel than placebo recipients (19.2 vs. 8.3 % in Study 304 [23]; 11.6 vs. 4.4 % in Study 305 [24]; 12.2–14.8 vs. 8.2 % in Study 306 [25]).

During the double-bind period in Study 305, there were 27 falls in 15 patients (6.0 %) in the perampanel groups compared with four falls among four patients (2.9 %) in the placebo group [24]. Although the other phase III trials did not specifically mention falls as an adverse event, the US prescribing information states that falls were reported in 5 and 10 % of patients randomized to perampanel 8 and 12 mg/day, respectively, compared with 3 % of placebo recipients, in the phase III trials [20]. Both the EU SmPC and the US prescribing information state that there appears to be an increased risk of falls with perampanel, especially in elderly patients [10, 20].

Interim results from the large ($n = 1186$) extension (Study 307 [27]) of the three phase III trials provide longer-term data on the tolerability profile of perampanel in patients with refractory partial-onset seizures. In this analysis, dizziness, somnolence, headache and fatigue were the most frequently reported treatment-emergent adverse events (see Fig. 5). In general, the longer-term tolerability profile of perampanel as adjunctive therapy was similar to that reported in the shorter-term phase III clinical trials. Almost half of the patients (48.9 %) received perampanel for >52 weeks and 21.1 % were exposed to perampanel for >76 weeks. The median duration of exposure to perampanel was 51.4 weeks and most patients (91.4 %) received perampanel dosages of 10 or 12 mg/day.

There were also no unexpected safety concerns in an interim report of Study 207, a long-term extension of the two phase II dose-escalation trials [36]. The open-label extension enrolled 138 patients and included a 12-week

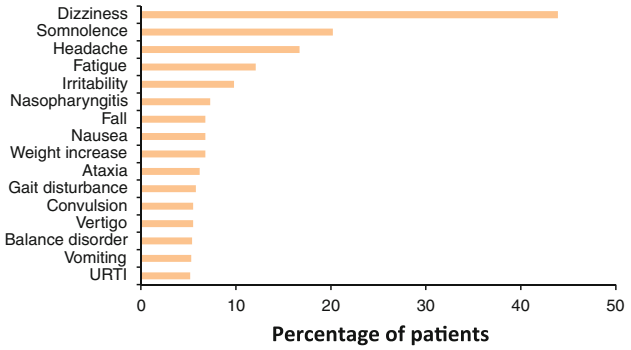

Fig. 5 Tolerability data from the extension of the clinical phase III trials (Study 307) [27]. Treatment-emergent adverse events occurring in at least 5 % of patients in the safety analysis set of 1186 individuals with refractory partial-onset seizures who completed the phase III trials and received perampanel for up to ≈2 years (median 51.4 weeks). Most patients received perampanel 10 or 12 mg/day (in addition to concurrent antiepileptic drugs). *URTI* upper respiratory tract infection

titration phase during which the dosage of perampanel was increased to 12 mg/day. Approximately 40 % of patients ($n = 57$) had >3 years' exposure to perampanel, including 18 individuals who received the drug for at least 4 years. Dizziness, headache and somnolence were the most frequently reported treatment-emergent adverse events.

The EU SmPC includes warnings or precautions about suicidal ideation (as this has been reported in patients treated with AEDs in various indications), aggression (cases have been reported with perampanel, more frequently at higher dosages) and abuse potential [10]. US prescribing information includes a boxed warning for serious psychiatric and behaviour reactions [20]. In the phase III trials with perampanel, suicidal ideation was reported in two patients receiving perampanel (one randomized to 8 mg/day in Study 304 and one randomized to 2 mg/day in Study 306) and two patients receiving placebo (one in Study 304 and one in Study 305) [23–25]. Interim results of the extension of the phase III trials reported six cases of suicidal ideation with perampanel (<1 %), including four patients who required hospitalization [27].

6 Dosage and Administration

Perampanel should be taken orally once daily at bedtime [10, 20]. In the EU, perampanel is available as film-coated tablets, which should be swallowed whole with a glass of water and may be taken with or without food [10]. Some aspects of dosage and administration recommendations vary between the EU [10] and the USA [20], and local prescribing information should be consulted.

The EU SmPC for perampanel states that, for its approved indication in adults and adolescents, the effective dosage range is 4–12 mg/day [10]. Perampanel should be initiated at a dosage of 2 mg/day and the dosage may be increased by increments of 2 mg/day to a maintenance dosage of 4–8 mg/day. Depending upon individual clinical response and tolerability at a dosage of 8 mg/day, the dosage may be increased by increments of 2 mg/day up to a maximum of 12 mg/day. Upward dosage titration should occur no more frequently than at 2-week intervals in the EU unless patients are receiving concomitant drugs that shorten the elimination half-life of perampanel (e.g. carbamazepine, oxcarbazepine, phenytoin), in which case upward dosage titration should occur no more frequently than at 1-week intervals [10].

US prescribing information states that the recommended dosage range for perampanel is 8–12 mg/day [20]. The starting dosage is 2 mg/day for those not receiving concurrent therapy with an enzyme-inducing AED, and upward dosage titration is usually achieved using 2 mg/day increments at weekly intervals (although 2-week intervals are recommended for elderly patients). In the USA, a starting dosage of 4 mg/day is recommended for patients receiving concurrent enzyme-inducing AEDs [20].

In elderly patients and those with mild renal impairment in the EU and in the USA, dosage adjustment of perampanel is not required [10, 20], aside from a slower titration rate for elderly compared with younger patients in the USA [20]. Perampanel is not recommended in patients with moderate or severe renal impairment, including those on haemodialysis [10, 20].

In patients with mild or moderate hepatic impairment the dosage should not exceed 8 mg/day in the EU [10]. The maximum recommended dosage of perampanel is 6 mg/day for patients with mild hepatic impairment and 4 mg/day for those with moderate hepatic impairment in the USA [20]. In both the EU and the USA, perampanel is not recommended in patients with severe hepatic impairment [10, 20].

Perampanel can have clinically significant interactions with various drugs (see Sect. 3.3). For more detailed information on drug interactions, use in special patient populations, warnings and precautions, local prescribing information should be consulted.

7 Perampanel: Current Status

Perampanel is the first in a new class of AED (AMPA receptor antagonists) and was recently approved in the EU and in the USA for the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. In three randomized, double-blind, placebo-controlled, phase III trials in patients with refractory partial-onset seizures,

once-daily administration of perampanel 4, 8 and 12 mg/day (6-week titration phase followed by 13-week maintenance phase), as adjunctive therapy with one to three AEDs, was statistically superior to adjunctive placebo in achieving the key efficacy endpoints of the percentage change from baseline in seizure frequency and/or the proportion of patients with a ≥50 % reduction in seizure frequency relative to baseline. Interim data from an extension of the three phase III trials (16-week blinded conversion period followed by open-label maintenance phase) showed a similar group response for the reduction in seizure frequency over at least 1 year of adjunctive treatment with perampanel. Perampanel was generally well tolerated over the longer-term in extension studies, with no unexpected adverse events reported. Results of these clinical trials, together with its unique mechanism of action, indicate that perampanel is a useful adjunctive treatment option in patients with refractory partial-onset seizures.

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