INTRODUCTION

Epilepsy is a serious neurological condition that affects more than 50 million individuals globally, 80% of whom live in developing countries. An estimated 1.7% of U.S. adults have been diagnosed with the condition. From prominent historical figures, such as Julius Caesar and Vladimir Lenin, to friends or family members, most people probably know someone affected by epilepsy.

Epileptic seizures (defined by two or more unprovoked seizures separated by more than 24 hours, or one unprovoked seizure with high probability of an additional seizure in the next 10 years, or as better defined by an epileptic syndrome) are separated into two broad categories: partial-onset seizures (POS) and generalized seizures, which affect one or both hemispheres of the brain, respectively. While many risk factors (e.g., infection, genetics, prenatal injury, or structural or metabolic abnormalities) have been elucidated, more than half of all cases of epilepsy are due to unknown causes. Regardless of the causative factor, epileptic seizures result from a persistent and uncontrolled increase in hypersynchronous neuronal excitability implicating various receptors (e.g., sodium, calcium, potassium, gamma-aminobutyric acid, or glutamate) involved in normal neurotransmission. Antiepileptic drugs (AEDs) target the various receptors to reduce neuronal excitability and control seizures, thus reducing the risk of seizure-related injuries and death. Although monotherapy is ideal for treating epileptic seizures, only about 49% of patients achieve seizure freedom while using their first appropriately selected AED. Subsequently, 62% to 66% of patients might only be able to achieve seizure freedom with a second or third appropriately selected AED, respectively, leaving up to one-third of patients with inadequate control of their seizures. In addition, patients may have a higher risk of toxicity if AEDs with similar mechanisms of action are used concomitantly. In the last two decades, the number of agents commercially available in the armamentarium against epilepsy has risen fourfold, few with a novel mechanism of action. The Food and Drug Administration approved perampanel (Fycompa, Eisai, Inc.) in October 2012 as an adjunctive agent for the treatment of POS with or without secondary generalization in patients with epilepsy at least 12 years of age. In June 2015, the agency approved a second indication for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy who are at least 12 years of age.

MECHANISM OF ACTION

Perampanel (2-[2-oxo-1-phenyl-5-pyrinid-2-yl-1,2 dihydropyrinid-3-yl] benzonitrile hydrate) is a novel non-competitive selective antagonist at the postsynaptic ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. In the nervous system, glutamate is known to be a major excitatory neurotransmitter, but the exact antiepileptic mechanism of perampanel in humans is unknown. Studies suggest that AMPA receptor antagonism can lead to reduced overstimulation and anticonvulsant effects, as well as inhibiting seizure generation and spread. In addition, AMPA receptor antagonists may prevent neuronal death.

PHARMACOKINETICS

Absorption

Administration of perampanel results in rapid and complete absorption with negligible first-pass metabolism. The median time to reach peak concentration varies between 0.5 to 2.5 hours fasting (delayed by two to three hours when taken with food). Peak plasma concentration is reached in approximately one hour (decreased by 40% when taken with food). It is worth noting that the extent of absorption is not affected by food.

Distribution

Fycompa is approximately 95% to 96% protein-bound in the concentration range of 20 ng/mL to 2,000 ng/mL.

Metabolism

Mediated by cytochrome P450 (CYP) 3A4/5, CYP1A2, and CYP2B6, perampanel is metabolized extensively through oxidation followed by glucuronidation based on in vitro results. Radiolabeled perampanel administration resulted in approximately 30% and 70% of oxidative and conjugated metabolites being found in urine and feces, respectively.

Elimination

The half-life of perampanel is approximately 105 hours in patients who are not concomitantly taking an enzyme-inducing AED, allowing for steady state to be reached in two to three weeks. Clearance rates for adult males (0.730 L per hour) and females (0.605 L per hour) were similar to those of patients less than 18 years of age (0.787 L per hour).

CLINICAL TRIALS

Clinical trials of perampanel have been conducted with patients diagnosed with PGTC seizures, and with those undergoing uncontrolled, drug-resistant, or refractory POS. These trials are summarized in Table 1. In all studies, the primary efficacy endpoint was the percent change in seizure frequency per 28 days.
### Table 1 Summary of Clinical Trials of Perampanel

<table>
<thead>
<tr>
<th>Locations and dates</th>
<th>French et al.19</th>
<th>French et al. Study 304&lt;sup&gt;23&lt;/sup&gt;</th>
<th>French et al. Study 305&lt;sup&gt;23&lt;/sup&gt;</th>
<th>Krauss et al. Study 306&lt;sup&gt;44&lt;/sup&gt;</th>
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<tr>
<td>78 sites in Australia, Austria, China, Czech Republic, France, Germany, Greece, India, Israel, Japan, Latvia, Lithuania, Poland, Serbia, South Korea, and the U.S. September 2011–May 2014</td>
<td>68 centers across Argentina, Canada, Chile, Mexico, and the U.S. April 2008–November 2010</td>
<td>78 sites in Australia, Austria, Belgium, Germany, Finland, France, United Kingdom, Greece, India, Israel, Italy, The Netherlands, Russia, Sweden, South Africa, and the U.S. May 2008–January 2011</td>
<td>116 centers in Germany, Bulgaria, Portugal, Lithuania, India, and China August 2008–May 2010</td>
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#### Study subjects<sup>a</sup>

| Study subjects<sup>a</sup> | 163 patients with PGTC and idiopathic generalized epilepsy | 388 patients with POS with or without secondary generalization who had failed ≥ 2 AEDs, had ≥ 5 partial seizures during baseline, and were taking stable doses of up to 3 approved AEDs | 386 patients with simple or complex POS with or without secondary generalization who failed ≥ 2 AEDs, had ≥ 5 partial seizures during baseline without a 25-day seizure-free period, and were taking stable doses of up to 3 approved AEDs | 706 patients with simple or complex POS with or without secondary generalization who had uncontrolled POS despite treatment with at least 2 different AEDs in prior 2 years |

#### Primary objective

| Primary objective | Assess efficacy of adjunctive PER in patients with drug-resistant PGTC associated with idiopathic generalized epilepsy | Assess efficacy and safety of once-daily 8 mg or 12 mg PER when added to concomitant AEDs in the treatment of POS | Assess the efficacy and safety of once-daily 8 mg and 12 mg PER when added to 1–3 concomitant AEDs in patients with uncontrolled POS | Assess efficacy and safety of once-daily 2 mg, 4 mg, and 8 mg PER added to 1–3 concomitant AEDs in patients with uncontrolled POS |

#### Study design

| Study design | Randomized, multicenter, double-blind, PBO-controlled, parallel-group study comparing 8 mg or highest tolerated dose of oral PER with oral PBO | Randomized, multicenter, double-blind, PBO-controlled, parallel-group study comparing once-daily 8 mg or 12 mg oral PER with oral PBO | Randomized, multicenter, double-blind, PBO-controlled study comparing once-daily 2 mg, 4 mg, and 8 mg oral PER with oral PBO |

#### Primary efficacy endpoint

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Percent change in seizure frequency per 28 days</th>
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<tr>
<td>Primary endpoint results</td>
<td>Statistically significant median percent change for seizure frequency with PER vs. PBO (–76.5% vs. –38.4%; P &lt; 0.0001)</td>
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#### Secondary efficacy endpoint(s)

<table>
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<tr>
<th>Secondary efficacy endpoint(s)</th>
<th>50% responder rate</th>
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<tr>
<td>Secondary efficacy endpoint results</td>
<td>Statistically significant 50% responder rate for PER vs. PBO (64.2% vs. 39.5%; P = 0.0019)</td>
<td>Statistically significant 50% responder rate for 8 mg and 12 mg PER vs. PBO (37.6% and 36.1%, respectively, vs. 26.4%; P = 0.0176 and P = 0.0914)</td>
<td>Statistically significant 50% responder rate for 8 mg and 12 mg PER vs. PBO (33.3% and 33.9%, respectively, vs. 14.7%; P = 0.002 and P &lt; 0.001)</td>
</tr>
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</table>

#### Secondary efficacy endpoint results

| Adverse events<sup>b</sup> | Dizziness (32.1%), fatigue (14.8%), headache (12.3%), somnolence (11.1%), and irritability (11.1%) | Dizziness (8 mg, 37.6%; 12 mg, 38.1%), somnolence (18%; 17.2%), irritability (7.5%; 14.2%), fatigue (15%; 13.4%), falls (9.8%; 12.7%), and ataxia (6%; 11.9%) | Dizziness (8 mg, 32.6%; 12 mg, 47.9%), somnolence (12.4%; 18.2%), fatigue (13.2%; 16.5%), and headache (8.5%; 13.2%) | Dizziness (2 mg, 10%; 4 mg, 16.3%; 8 mg, 26.6%), somnolence (12.2%; 9.3%; 16%), and headache (8.9%; 11%; 10.7%) |

AED = antiepileptic drug; ILEA = International League Against Epilepsy; NP = not published; PBO = placebo; PER = perampanel; PGTC = primary generalized tonic-clonic seizures; POS = partial-onset seizures.

<sup>a</sup> All patients were 12 years of age or older and were diagnosed using ILEA criteria.

<sup>b</sup> Most frequently reported in 10% or more of patients.
Table 1 Summary of Clinical Trials of Perampanel (continued)

<table>
<thead>
<tr>
<th>Locations and dates</th>
<th>Krauss et al. Study 307&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Steinhoff et al. Pooled Analysis of 304, 305, and 306&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Vazquez et al. Pooled Subanalysis of 304, 305, and 306&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study subjects&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,218 patients (from those who completed the double-blind phase of studies 304, 305, and 306) with uncontrolled simple or POS with or without secondary generalization despite treatment with 1–3 approved AEDs</td>
<td>1,478 patients with refractory POS despite treatment with 1–3 approved AEDs</td>
<td>1,478 patients (719 males, 759 nonpregnant females) with drug-resistant POS with or without secondary generalization despite treatment with 1–3 AEDs in prior 2 years</td>
</tr>
<tr>
<td>Primary objective</td>
<td>Assess safety, tolerability, and seizure outcome data for long-term treatment with adjunctive PER for refractory POS</td>
<td>Assess efficacy and safety of adjunctive PER</td>
<td>Assess efficacy and tolerability of adjunctive PER by gender</td>
</tr>
<tr>
<td>Study design</td>
<td>Multicenter, randomized, double-blind, PBO-controlled, parallel-group study comparing 12 mg or highest tolerated dose of oral PER with oral PBO</td>
<td>Randomized, multicenter, double-blind, PBO-controlled study comparing once-daily 4 mg, 8 mg, and 12 mg oral PER with oral PBO</td>
<td>Randomized, multicenter, double-blind, PBO-controlled, parallel-group study comparing once-daily 2 mg, 4 mg, 8 mg, or 12 mg oral PER with oral PBO</td>
</tr>
<tr>
<td>Primary efficacy endpoint</td>
<td>Percent change in seizure frequency per 28 days over 2 years</td>
<td>Percent change in seizure frequency per 28 days</td>
<td>Percent change in seizure frequency per 28 days</td>
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<tr>
<td>Primary endpoint results</td>
<td>Percent change in seizure frequency per 28 days over 2 years (in weeks): 1–13: –29.1% (n = 1,207) 14–26: –39.2% (n = 1,114) 27–39: –44% (n = 979) 40–52: –46.5% (n = 731) 53–65: –51.2% (n = 495) 66–78: –52.3% (n = 323) 79–91: –51.2% (n = 176) 92–104: –58.1% (n = 59)</td>
<td>Statistically significant percent change for seizure frequency with PER 4 mg, 8 mg, and 12 mg vs. PBO (–23.3%, –28.8%, and –27.2%, respectively, vs. –12.8%; P &lt; 0.01, each dose vs. PBO).</td>
<td>Statistically insignificant percent change for seizure frequency greater in females than males with PER 4 mg and 12 mg vs. PBO; statistically significant median percent change for seizure frequency greater in females than males with PER 8 mg (female, 35%; male, 22%; P &lt; 0.05)</td>
</tr>
<tr>
<td>Secondary efficacy endpoint(s)</td>
<td>50% responder rate over 2 years</td>
<td>50% responder rate</td>
<td>50% responder rate</td>
</tr>
<tr>
<td>Secondary endpoint results</td>
<td>50% responder rate for PER over 2 years (in weeks): 1–13: 31.1% (n = 1,207) 14–26: 41.4% (n = 1,114) 27–39: 45.3% (n = 979) 40–52: 46.9% (n = 731) 53–65: 50.7% (n = 495) 66–78: 51.1% (n = 323) 79–91: 51.7% (n = 176) 92–104: 62.7% (n = 59)</td>
<td>Statistically significant 50% responder rate for 4 mg, 8 mg, and 12 mg PER vs. PBO (28.5%, 35.3%, and 35%, respectively, vs. 19.3%; P &lt; 0.05, each dose vs. PBO). Statistically significant percent change for frequency of complex partial plus secondary generalized seizures for 4 mg, 8 mg, and 12 mg PER vs. PBO (–31.2%, –35.6%, and –26.8%, respectively, vs. –13.9%; P &lt; 0.001)</td>
<td>Statistically insignificant 50% responder rate greater for females than males for 4–12 mg PER</td>
</tr>
<tr>
<td>Adverse events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dizziness (43.9%), somnolence (20.2%), headache (16.7%), and fatigue (12.1%)</td>
<td>Dizziness (4 mg, 16.3%; 8 mg, 31.8%; 12 mg, 42.7%), somnolence (9.3%;15.5%; 17.6%), headache (11%;11.4%; 13.3%), fatigue (7.6%; 8.4%; 12.2%), and falls (7.1%; 5.1%; 10.2%)</td>
<td>Dizziness (female, 31.5%; male, 24.4%), somnolence (14.3%; 14.6%), and headache (13.2%; 9.4%)</td>
</tr>
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</table>

AED = antiepileptic drug; ILEA = International League Against Epilepsy; NP = not published; PBO = placebo; PER = perampanel; PGTC = primary generalized tonic-clonic seizures; POS = partial-onset seizures.

<sup>a</sup> All patients were 12 years of age or older and were diagnosed using ILEA criteria.

<sup>b</sup> Most frequently reported in 10% or more of patients.
and a common secondary efficacy endpoint was the 50% responder rate. In the 2015 clinical trial conducted by French et al., patients with PGTC seizures who were taking 8 mg or the highest tolerated dose of perampanel showed a statistically significant reduction in the frequency of seizures compared with placebo (–76.5% versus –38.4%; P < 0.0001). The study also demonstrated that the number of patients achieving a 50% or more reduction in PGTC seizure frequency (50% responder rate) was statistically significant for patients taking perampanel (64.2% versus 39.5%; P = 0.0019).

In Study 304, the efficacy and safety of once-daily 8-mg and 12-mg perampanel were assessed for patients with POS with or without secondary generalization who did not respond to at least two AEDs, had at least five partial seizures at baseline, and were on stable doses of up to three approved AEDs. Results showed a statistically significant reduction in the frequency of seizures for patients on 8-mg and 12-mg perampanel compared with placebo (–26.3% and –34.5%, respectively, versus –21%; P = 0.0261 and P = 0.0158). The study’s secondary efficacy endpoint was patients achieving at least a 50% reduction in POS frequency (50% responder rate). Results for the 50% responder rate were not statistically significant for patients taking perampanel (37.6% and 36.1%, respectively, versus 39.5%; P = 0.0760 and P = 0.0914).

Study 304 had an additional secondary efficacy endpoint: the percent change in the 28-day frequency of complex partial plus secondarily generalized seizures. Those results showed a statistically significant percent change for 8 mg and 12 mg versus placebo (–23.3% and –30.8%, respectively, versus –10.7%; P = 0.003 and P < 0.001), but the change was not statistically significant for 2 mg (–13.6%; P = 0.420). The study also demonstrated that the number of patients achieving a 50% or greater reduction in POS frequency (50% responder rate) was statistically significant for 4 mg and 8 mg versus placebo (28.5% and 34.9%, respectively, versus 17.9%; P = 0.013 and P < 0.001), but was statistically insignificant for 2 mg (20.6%; P value not published).

As an additional secondary efficacy endpoint, Study 306 evaluated the percent change in the 28-day frequency of complex partial plus secondarily generalized seizures and found a statistically significant percent change with perampanel 4 mg and 8 mg versus placebo (–31.2% and –38.7%, respectively, versus –17.6%; P = 0.007 and P < 0.001), but the change was not statistically significant for 2 mg (–20.5%; P value not published).

Study 307 extended Studies 304, 305, and 306 to assess the safety, tolerability, and seizure outcome data for long-term treatment with adjunctive perampanel for refractory POS. The primary efficacy endpoint was percent change in seizure frequency per 28 days over a two-year period. Results showed a sustained reduction in seizure frequency for patients who had at least 26 weeks, 39 weeks, one year, and two years of exposure to perampanel. The percent change in seizure frequency was recorded for every 13-week interval (Table 1). The study also demonstrated that the rate of patients achieving at least a 50% reduction in POS frequency (50% responder rate) was statistically significant for patients taking perampanel 4 mg, 8 mg, and 12 mg versus placebo (–23.3%, –28.8%, and –27.2%, respectively, versus –12.8%; P < 0.01 for each dose versus placebo).

Vazquez et al. conducted a pooled analysis of Studies 304, 305, and 306 to assess the efficacy and tolerability of adjunctive perampanel by gender. The primary efficacy endpoint was the percent change in seizure frequency per 28 days, and results showed a statistically significant difference in gender only at 8 mg, with female efficacy greater than male efficacy (female, 35%; male, 22%; P < 0.05). The 50% responder rate was a secondary efficacy endpoint, and results showed the difference between genders to be statistically insignificant.

**INDICATIONS AND DOSING**

Perampanel is indicated in patients with epilepsy who are 12 years of age and older for the treatment of POS with or without secondary generalization and for the treatment of PGTC seizures, in both cases as an adjunctive agent.

The recommended starting dose of perampanel for POS and PGTC seizures in patients not concomitantly taking an enzyme-inducing AED is 2 mg by
mouth at bedtime. Titrate by 2 mg daily at weekly intervals. The recommended dosage range for patients with POS in the absence of enzyme-inducing AEDs is 8 mg to 12 mg at bedtime, while in patients with PGTC seizures the recommended maintenance dose is 8 mg at bedtime. Dosing should be individualized and based on the patient’s clinical response and tolerability.

For patients with POS and PGTC seizures concomitantly taking an enzyme-inducing AED (including but not limited to phenytoin, carbamazepine, and oxcarbazepine), the recommended initial dose is 4 mg of perampanel once a day at bedtime. Titrate by 2 mg daily at weekly intervals. The maximum dose in the presence or absence of concomitant enzyme-inducing AEDs is 12 mg at bedtime.

In patients with hepatic impairment, perampanel should be initiated at 2 mg once a day at bedtime and titrated by no more than 2 mg every two weeks. The maximum recommended doses for patients with mild and moderate hepatic impairment are 6 mg and 4 mg, respectively. In patients with moderate renal impairment, close monitoring and slower titration is recommended. Perampanel is not recommended in the setting of severe hepatic or severe renal impairment or in patients undergoing hemodialysis.

In the event of a single missed dose, patients may wait to take their next dose as regularly scheduled. Perampanel may be restarted at the last given dose for patients who have missed more than one dose continuously for less than three weeks (one week for patients concomitantly taking enzyme-inducing AEDs). For patients who have discontinued the use of perampanel for more than three weeks, initial dosing recommendations should be followed. Perampanel should be reduced gradually when considering discontinuation because of a potential increase in seizure frequency, but abrupt cessation may be attempted if needed due to its long half-life. In the event of a perampanel overdose, supportive care is indicated. Forced diuresis, dialysis, or hemoperfusion may not be of value due to the medication’s poor renal clearance.

**ADVERSE DRUG REACTIONS**

Based on pooled analysis of three placebo-controlled trials with 858 patients with POS taking perampanel versus 422 patients taking a placebo, the most common adverse reactions (at least 5%) were dizziness, somnolence, headache, irritability, fatigue, falls, ataxia, nausea, vertigo, and back pain (Table 2).

In a study population of patients with PGTC seizures (n = 163), the most common adverse effects seen in patients taking perampanel 8 mg versus placebo were dizziness, fatigue, headache, somnolence, irritability, vertigo, vomiting, weight gain, confusion, nausea, abdominal pain, and anxiety (Table 3).

**WARNINGS AND PRECAUTIONS**

Patients should be monitored for serious psychiatric and behavioral reactions. In the POS clinical trials, dose-related adverse reactions related to hostility and aggression were reported in 20%, 12%, and 6% of patients taking perampanel 12 mg, perampanel 8 mg, and placebo, respectively (Table 4). Homicidal ideation and/or threat was seen in 0.1% of 4,368 patients in controlled or open-label trials for epilepsy and other conditions. Belligerence, affect lability, agitation, and physical assault were more common with perampanel, although percentages were not reported in clinical trials. These events can occur with or without prior psychiatric histories, aggressive behavior, or use of other medications associated with hostility or aggression. Patients with pre-existing psychiatric conditions may experience a worsening of their psychiatric condition while taking perampanel. Concomitant use of perampanel with alcohol should be avoided, as it significantly worsened mood and increased anger. Additionally, AEDs as a class may increase the risk of suicidal ideation or behavior for any indication, and patients taking them should be...
monitored for unusual changes in mood or behavior. 

No contraindications are listed for the medication.

Pregnancy and Lactation

This medication is classified as pregnancy category C, indicating it may cause fetal harm based on animal studies; however, due to the lack of well-controlled studies in pregnant women, the risk is uncertain. Administration of perampanel during organogenesis in rats and rabbits resulted in diverticulum of the intestine, reduced fetal body weight, and embryolethality. In addition, perampanel and/or its metabolites can be found in rat milk in concentrations higher than serum; however, it is unknown if perampanel is excreted in human milk. Caution is advised when considering the use of perampanel in women who are of childbearing age or who may be pregnant or nursing.6,8

DRUG INTERACTIONS

The concomitant use of central nervous system depressants such as alcohol, benzodiazepines, narcotics, barbiturates, and sedating antihistamines may cause additive central nervous system depression. Patients are advised not to drive or operate machinery until they have gained experience with perampanel. At doses of 12 mg per day, perampanel can reduce levonorgestrel serum levels by 40%, thus rendering contraceptives containing levonorgestrel less effective. CYP3A4 enzyme inducers (e.g., carbamazepine, phenytoin, oxcarbazepine) can decrease perampanel plasma concentrations by 20–50% and may require dose adjustment. In addition, concomitant medications, and comorbid conditions is essential when initiating and titrating perampanel. Patients and caregivers should be educated on the common adverse effects and precautions of using perampanel and should report any changes in mood or behavior to their prescriber.8,9

CONCLUSION

Perampanel is a safe and effective adjunctive treatment option for patients with POS and PGTC seizures. Additional evidence suggests perampanel may also be useful in refractory POS, but less useful for drug-resistant POS. Careful monitoring of the patient’s clinical status, concomitant medications, and comorbid conditions is essential when initiating and titrating perampanel. Patients and caregivers should be educated on the common adverse effects and precautions of using perampanel and should report any changes in mood or behavior to their prescriber.

REFERENCES