despite best medical management with available anti-seizure medications, approximately 20-40 percent of patients with epilepsy remain refractory to available anti-epileptic drugs. Therefore, newer pharmacological agents with novel mechanisms have been sought to address the unmet need. Perampanel (Fycompa, Eisai, Inc.) is recently available for use in the United States and has been in use in Germany since September of 2012. Based on data from three randomized clinical trials, perampanel was approved for adjunctive treatment of patients who suffer from partial epilepsy with or without secondary generalization who are at least 12 years old.\textsuperscript{1,2}

**MECHANISM**

Perampanel has a novel mechanism of action. Perampanel (PER) is a first in class orally active, selective, non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonist.\textsuperscript{3} AMPA receptors are postsynaptic ionotropic excitatory receptors with glutamate binding sites.\textsuperscript{3} AMPA receptors are thought to participate in the induction of seizures by synchronizing excitatory glutamatergic signaling.\textsuperscript{4} Preclinical trials found perampanel to be effective in preventing seizures in models of partial onset and generalized seizures including: maximal electroshock model, audiogenic seizure model, pentylenetetrazol induced seizure model, amygdaloid kindling model and 6 Hz electroshock model.\textsuperscript{1,4} In vitro, perampanel was found to inhibit AMPA mediated increase in intracellular calcium that was concentration dependent which is thought to reduce neuronal excitability.\textsuperscript{4,5} The effect of perampanel in vitro on NMDA receptors was present but not significant.\textsuperscript{4} In mouse models of tonic clonic generalized seizures and absence seizures PER proved more potent at preventing seizures than carbamazepine and sodium valproate, and there was evidence of synergism with phenytoin, carbamazepine and valproate.\textsuperscript{4}

**CLINICAL TRIALS**

Primary support of the approval of PER came from three phase three clinical trials, specifically identified as 304, 305 and 306. These studies were used to identify a minimum effective dose and establish an effective dose range.\textsuperscript{7} All studies used an experimental group consisting of patients with refractory epilepsy despite one to three antiepileptic drugs.\textsuperscript{5,6,7} All studies involved a six week baseline phase for collection of baseline seizure data followed by a six week titration and 13 week maintenance phase.\textsuperscript{5,6,7} End points were 50 percent responder rate and percent change in seizure frequency.\textsuperscript{5,6,7}

**Trial 304.** Three-hundred-eighty-eight patients were randomized in a 1:1:1 ratio to 8mg perampanel daily, 12mg perampanel daily, or placebo. Median percent change in seizure frequency and 50 percent responder rate for the 8mg group were -26.3% and 37.6% and -34.5% and 36.1% for the 12mg group, which showed improvement over placebo.\textsuperscript{6}

**Trial 305.** Three-hundred-eighty-six patients were randomized in a 1:1:1 ratio to 8mg perampanel daily, 12mg perampanel daily, or placebo.\textsuperscript{7} Median percent change in seizure frequency and 50 percent responder rates were -30.5% and 33.3% for the 8mg dose and -33.9% and -17.6% for 12mg dose.\textsuperscript{7} Both the 8mg and 12mg doses showed improvement over placebo.\textsuperscript{7}
Trial 306. Seven-hundred-six patients were randomized in a 1:1:1:1 ratio to 2mg, 4mg, 8mg of perampanel daily or placebo. Median percent change in seizure frequency and 50 percent responder rates were: -13.6% and 20% for the 2mg dose, -23.3%, 28.5% for the 4mg dose, and -30.8% and 34.9% for the 8mg dose. Responses were significant when compared to placebo for the 4mg and 8mg daily doses. The 2mg dose was not statistically different in comparison to placebo.

In total, these studies support a dose responsive reduction in seizure burden for PER at doses of 4-12mg per day.

PHARMACOLOGY

PER has a long half-life of 70-120 hours, which allows for once daily dosing. Recommended dose ranges from 4-12mg based on the above referenced clinical trials. PER is rapidly and completely absorbed following oral administration. Steady state plasma concentrations are achieved within 14 days following oral administration. Protein binding is 95%. PER has significant metabolism via the p450 system, therefore; concentration of PER may be significantly reduced in the presence of P450 inducers, such as phenytoin or carbamazepine. However, PER is not thought to affect plasma concentration of other anti epileptic drugs. In animal models, there has not been any significant impact on fertility nor have any teratogenic effects been identified. Initiating therapy with perampanel requires stepwise titration. Starting dose of PER is 2mg daily for patients not on inducing AEDs and 4mg daily for patients on inducing agents. PER may be increased by 2mg weekly to a total dose of 12mg daily depending on tolerability and seizure control. Titration should be slowed in patients who are elderly or have mild to moderate hepatic impairment. PER is not recommended for patients with severe renal or hepatic failure.

SIDE EFFECTS

Side effects are consistent with those seen in other anti-epileptic drugs and consist mainly of dizziness, somnolence, diplopia, ataxia. During the three phase III treatment trials the most common treatment emergent side effects were dizziness, somnolence, ataxia, headache and irritability. Worsening seizures, defined as >50% increased compared to baseline, were seen in eight to 11 percent of patients treated with 2-12mg of PER compared with 10-15 percent increase in the placebo groups. Weight increase was noted above that of the placebo population. With the exception of weight gain, adverse effects were noted to be dose-dependent. Dizziness and somnolence were the most common side effects prompting drug discontinuation or dose reduction. Of particular note, given the mechanism of action, psychiatric adverse effects did not include behavioral events, such as those seen with pcp intoxication. However, psychiatric AEs did include insomnia, anxiety, aggression, confusional state, and anger. No significant EKG changes were noted.

EXPERIENCE TO DATE

Perampanel was available for use in Germany ahead of the US. Early experience with 74 patients with add-on perampanel was reported from September of 2012 through June of 2013. This population was noted to be refractory to multiple other drugs, epilepsy surgery and neuro-stimulation, and included multiple seizure types specifically: LGS, structural and metabolic, and idiopathic. The patients in this study were taking between one and four antiepileptic drugs at baseline. In this difficult to react population, the authors report a 46 percent responder rate as determined by a seizure reduction of 50 percent or more. Adverse events were primarily dizziness and somnolence as predicted by earlier trials.

More recently, Krauss et al. reported global safety results for patients participating in extension study 307. This study followed over 1,200 patients who had previously completed one of three phase III treatment trials for PER. The patients were titrated to their maximum tolerated dose followed by open label maintenance. No new safety concerns were seen and reductions in seizure frequency were stable for patients with up to three years of exposure to PER.

CONCLUSION

PER is a newly available antiepileptic drug with a novel mechanism that has shown promise in clinical trials and early clinical use. Efficacy is similar to and side effects are consistent with other previously approved AEDs.

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