



## PDL NEW DRUG REVIEW

**Proprietary Name:** Fycompa®

**Common Name:** perampanel

**PDL Category:** Anticonvulsants

<u>Comparable Products</u>	<u>Preferred Drug List Status</u>
Lamotrigine	Preferred
Levetiracetam	Preferred
Topiramate	Preferred

### Summary

**Indications and Usage:** For adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy. This is a pregnancy category C medication. It is recommended that pregnant patients taking Fycompa® enroll in the North America Antiepileptic Drug (NAAED) Pregnancy Registry to provide information regarding the effects of *in utero* exposure. The safety and efficacy of use in children under the age of 12 years have not been established.

**Drug Interactions:** Concomitant use of Fycompa® with oral contraceptives may render them less effective; therefore, additional non-hormonal forms of contraception are recommended. In the presence of enzyme-inducing antiepileptics (AEDs; including carbamazepine, phenytoin, or oxcarbazepine), the starting dose of Fycompa® should be increased. Additionally, dose adjustments of Fycompa® may be needed if enzyme-inducing AEDs are initiated or withdrawn from a patient's regimen. Concomitant use of Fycompa® with other strong CYP3A4 inducers (i.e. rifampin, St. John's wort) should be avoided. The concomitant use of Fycompa® and CNS depressants, including alcohol, may increase CNS depression. In addition, patients should be counseled to not drive or operate machinery until they have gained enough experience on Fycompa® to determine how it affects these activities.

**Dosage Forms:** Tablets: 2mg, 4mg, 6mg, 8mg, 10mg, and 12 mg

**Recommended Dosage:** In the absence of enzyme-inducing antiepileptic drugs, the recommended starting dose is 2mg once daily at bedtime, with a dose titration no more than every 2 weeks. The recommended dose range is 8-12mg once daily. Individual dosing should be adjusted based on clinical response and tolerability.

In the presence of enzyme-inducing antiepileptic drugs, including phenytoin, carbamazepine, and oxcarbazepine, the recommended starting dose is 4mg once daily at bedtime. Patients should be closely monitored for response. If the enzyme-inducing AED is withdrawn or initiated, closely monitor for clinical response and tolerability. Dose adjustments may be needed.

Use is not recommended in those with severe hepatic or renal impairment or in those undergoing hemodialysis. Fycompa® should be used with caution in those with moderate renal impairment. Additionally, slower titration

should be considered. Dose adjustments are not required in those with mild renal impairment. Dose adjustments are recommended in those with mild or moderate hepatic impairment. The starting dose should be 2mg per day and titrated until target dose is achieved, up to a maximum recommended dose of 6mg in those with mild impairment and 4mg in those with moderate hepatic impairment.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Fycompa® 8mg) minus reported % incidence for placebo.* The most commonly reported adverse events with Fycompa® include vertigo (2%), blurred vision (2%), nausea (1%), constipation (0%), contusion (1%), skin laceration (1%), weight gain (3%), arthralgia (2%), pain in extremity (1%), asthenia (1%), ataxia (3%), balance disorder (4%), dizziness (23%), dysarthria (3%), fatigue (3%), gait disturbance (3%), confusional state (<1%), hypersomnia (2%), somnolence (9%), aggression (1%), anxiety (2%), irritability (4%), and oropharyngeal pain (1%).

Weight gain has been reported in adult clinical trials. There was an average of 1.1kg weight gain with Fycompa® as compared with 0.3kg with the placebo group over a median of 19 weeks. Furthermore, the percentage who gained at least 7% and 15% of their baseline body weight was 9.1% and 0.9%, respectively, with Fycompa® vs 4.5% and 0.2%, respectively, with placebo. Therefore, it is recommended to clinically monitor weight during treatment.

Fycompa® has a box warning regarding the increased risk of serious life-threatening psychiatric and behavioral reactions, including aggression, hostility, irritability, anger, and homicidal ideation and threats. These have been reported in patients taking Fycompa®. It is recommended to closely monitor patients, especially during the titration period and when taking higher doses, as well as to advise patients/caregivers to monitor for changes in mood, behavior, or personality that are not typical for the patient while taking Fycompa®. If symptoms occur, the dose of Fycompa® should be reduced, or discontinued if symptoms are severe or worsening.

**Contraindications:** There are currently no contraindications with this product.

**Manufacturer:** Eisai Inc.

**Analysis:** Perampanel, the active ingredient of Fycompa®, is a non-competitive antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the chief excitatory neurotransmitter in the CNS, and is implicated in a number of neurological disorders caused by neuronal over excitation. Nevertheless, the exact mechanism by which Fycompa® exerts its effects as an antiepileptic is not known. Perampanel (Fycompa®) has been designated by the DEA as a Schedule III of the Controlled Substance Act.

There were 3 multicenter, randomized, double-blind, placebo-controlled trials to assess the safety and efficacy of Fycompa® in those with partial-onset seizures, with or without secondary generalization, who were not adequately controlled with 1-3 concomitant AEDs. During the trials, >85% were taking 2-3 concomitant AEDs, while about 50% were taking  $\geq 1$  AED known to induce CYP3A4. The primary endpoint in Studies 1, 2, and 3 was the percent change in seizure frequency per 28 days during the treatment period as compared to the baseline period.

Results in Study 1 suggested statistical significance between Fycompa® 8mg and 12mg vs placebo. The median treatment effect (drug minus placebo) was -13.5% with the 8mg dose ( $p=0.0261$ ) and -14.2% with the 12mg dose ( $p=0.0158$ ). In Study 2, the median treatment effect was -19.1% with the 8mg dose ( $p=0.0008$ ) and -13.7% with the 12mg dose ( $p=0.0105$ ). In Study 3, the median treatment effect was -4.4% with the 2mg dose ( $p=0.4197$ , which is not statistically significant), -13.7% with the 4mg dose ( $p=0.0026$ ), and -20.1% with the 8mg dose ( $p<0.0001$ ).

The following table depicts the median treatment effect (drug minus placebo) for the combined studies based on the presence or absence of Fycompa® used concomitantly with inducing AEDs (carbamazepine, oxcarbazepine, and phenytoin).

Daily Dose	Median % Reduction from placebo		Responder Rate (Drug minus placebo)	
	Without Inducers	With Inducers	Without Inducers	With Inducers
2mg/day	8.2%	0.5%	6.3%	1.9%
4mg/day	15.3%	11.9%	15.4%	8.1%
8mg/day	25.7%	14.4%	28.2%	13.0%
12mg/day	33.2%	19.2%	39.3%	12.3%

The percentage of patients with a 40 to <60% reduction in seizure frequency was 13.3% for placebo vs 17.4%, 19%, and 15.8% for the 4mg, 8mg, and 12mg doses, respectively. The percentage of patients with ≥50% reduction in seizure frequency was 19.3% for placebo vs 28.5%, 35.3%, and 35% for the 4mg, 8mg, and 12mg doses, respectively.

A 2013 systematic review and meta-analysis by Hsu et al<sup>2</sup> included 5 randomized, placebo-controlled trials (N=1678) to assess the safety and efficacy of perampanel for the treatment of partial-onset epilepsy. The 50% responder rates were significantly greater in those taking the 4mg, 8mg, and 12mg perampanel doses vs placebo, with a risk ratio (RR) of 1.54 for the 4mg dose (CI 1.11-2.13), 1.80 for the 8mg dose (CI 1.38-2.35), and 1.72 for the 12mg dose (CI 1.17-2.52). Dizziness and somnolence were statistically associated with the 8mg dose while dizziness was statistically associated with the 12mg dose.

A 2013 systematic review and Bayesian network meta-analysis by Khan et al<sup>3</sup> included 12 randomized controlled trials to assess the safety and efficacy of perampanel as compared with placebo and other recently approved AEDs (including lacosamide, retigabine, and eslicarbazepine) for the adjunctive treatment of partial onset seizures with or without secondary generalization. There were 3 included studies for the four AEDs.

Results suggested that perampanel was significantly better than placebo for the responder rate (odds ratio [OR] 2.151, CI 1.348-3.472) and seizure freedom (OR 2.507, CI 1.067-7.429). When perampanel was compared with other AEDs, perampanel was found to be equally effective. Additionally, although perampanel had a statistically significantly greater withdrawal as compared with placebo, it had the lowest OR for withdrawal due to adverse events vs placebo compared with other AEDs.

There is no evidence at this time to support that Fycompa® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Fycompa® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

**PDL Placement:**       Preferred  
 Non-Preferred  
 Preferred with Conditions

## References

<sup>1</sup> Fycompa [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2012.

<sup>2</sup> Hsu WW, Sing CW, He Y, et al. Systematic review and meta-analysis of the efficacy and safety of perampanel in the treatment of partial-onset epilepsy. *CNS Drugs*. 2013; 27(10): 817-27.

<sup>3</sup> Khan N, Shah D, Tongbram V, et al. The efficacy and tolerability of perampanel and other recently approved anti-epileptic drugs for the treatment of refractory partial onset seizure: a systematic review and Bayesian network meta-analysis. *Curr Med Res Opin*. 2013; 29(8): 1001-13.