Fycompa (perampanel)

STRENGTH	DOSAGE FORM	ROUTE	GPID
2, 4, 6, 8mg	tablet	oral	33271, 33272, 33273, 33274

MANUFACTURER

Eisai Inc.

INDICATION(S)

As adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older

DRUG CLASS

SEIZURE DISORDER; ANTICONVULSANTS

PLACE IN THERAPY

Fycompa is the first anticonvulsant that works as a non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutamate receptor antagonist. Glutamate is the most prevalent excitatory neurotransmitter and is thought to play a role in the generation and spread of seizures. There are two ionotropic glutamate receptors, AMPA and N-methyl-D-aspartae (NMDA). Felbamate and topiramate are thought to act in part through NMDA antagonism. Other anticonvulsants typically work by affecting voltage-dependent sodium channels, calcium currents, or the activity of the neurotransmitter, gamma-aminobutyric acid (GABA). Many anti-epileptic drugs (AEDs) are generically available and are also labeled for use as an adjunctive therapy for the treatment of partial-onset seizures such as levetiracetam, lamotrigine, tiagabine, oxcarbazepine, gabapentin, and zonisamide.

The selection of a specific AED for treating seizures must be individualized to consider drug effectiveness for the seizure type or types, potential adverse effects of the drug, interactions with other medications, comorbid medical conditions (especially but not limited to hepatic and renal disease), age and gender (including childbearing plans), lifestyle/patient preferences and cost.

About half of patients with a new diagnosis of epilepsy will become seizure free with the first AED prescribed. Treatment failure may result from breakthrough seizures or drug intolerance. When the initial drug failure is due to adverse effects, the second drug trial will be successful in half of patients. Substantially fewer patients (about 10 to 20 percent) will have a successful second drug trial if the initial failure was due to lack of efficacy. The chances of treatment success diminish incrementally with each successive drug trial. In patients who have failed monotherapy, seizure remission is achieved with combination therapy in only a small percentage (10 to 15 percent). Overall, up to 80 percent of patients can become seizure free on AED treatment. Fycompa utilization will most likely be reserved for patients that are unable to be controlled on multiple agents. In the clinical trials that supported the FDA approval 85% of patients were taking 2 to 3 concomitant AEDs.

EFFICACY

The efficacy of Fycompa in partial-onset seizures, with or without secondary generalization, was studied in patients who were not adequately controlled with 1 to 3 concomitant AEDs in 3 randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3) in adult and adolescent patients (aged 12 years and older). All trials had an initial 6-week baseline period, during which patients were required to have more than five seizures in order to be randomized. The baseline period was followed by a 19 week treatment period (consisting of a 6 week titration phase and a 13 week maintenance phase). Patients in these 3 trials had a mean duration of epilepsy of approximately 21 years and a median baseline seizure frequency ranging from 9.3 to 14.3 seizures per 28 days. During the trials, more than 85% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation, and approximately 50% were on at least one AED known to induce CYP3A4 (i.e. carbamazepine, oxcarbazepine, or phenytoin), an enzyme critical to the metabolism of Fycompa. 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. Dose response was statistically significant at 4 to 8 mg with little additional reduction in frequency at 12 mg per day.

Median Treatment Difference (Drug - Placebo) of the Percent Reduction from Baseline during the 19-Week Treatment Period.

Dosage Group	n	Median Baseline Frequency (per 28 days)	Median Treatment Effect (Drug-Placebo)	p value
Study 1				
8 mg/day	133	14.3	-13.5%	0.0261
12 mg/day	133	12.0	-14.2%	0.0158
Study 2				
8 mg/day	129	13.0	-19.1%	0.0008
12 mg/day	121	13.7	-13.7%	0.0105
Study 3				
2 mg/day	180	10.1	-4.4%	0.4197
4 mg/day	172	10.0	-13.7%	0.0026
8 mg/day	169	10.9	-20.1%	<0.0001

Obtained from the Fycompa Package Insert

Median Treatment Effect (drug - placebo) for Combined Studies (Study 1, 2 and 3) Based on the Presence or Absence of Concomitant FYCOMPA Inducing AEDs (carbamazepine, oxcarbazepine, phenytoin)[a]

	Median Percent Reduction From Placebo		Responder Rate [b] (Drug - Placebo)	
	Without Inducers	With Inducers	Without Inducers	With Inducers
2 mg/day	8.2%	0.5%	6.3%	1.9%
4 mg/day	15.3%	11.9%	15.4%	8.1%
8 mg/day	25.7%	14.4%	28.2%	13.0%
12 mg/day	33.2%	19.2%	39.3%	12.3%

[a]Patients from Latin American region are excluded because of a significant treatment-by-region interaction due to high placebo response.
[b]The proportion of patients with at least a 50% decrease in seizure frequency

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SAFETY

There is a black box warning stating that serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking on Fycompa. These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression. Patients and caregivers should closely monitor patients for changes in mood, behavior, or personality while taking or discontinuing Fycompa (particularly during the titration period and at higher doses). A health care provider should be contacted immediately to contact if any of these reactions if these symptoms occur.

Patients should also monitor for dizziness, gait disturbance, somnolence, and fatigue. Overall, the most frequently reported adverse reactions in patients receiving Fycompa at doses of 8 mg or 12 mg included dizziness (36%), somnolence (16%), fatigue (10%), irritability (9%), falls (7%), nausea (7%), ataxia (5%), balance disorder (4%), gait disturbance (4%), vertigo (4%), and weight gain (4%). For almost every adverse reaction, rates were higher on 12 mg and more often led to dose reduction or discontinuation. The rate of discontinuation as a result of an adverse reaction was 3%, 8% and 19% in patients randomized to receive Fycompa at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 5% in patients randomized to receive placebo.

Fycompa is classified as a pregnancy category C. Physicians are advised to recommend that pregnant patients taking Fycompa enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

Strong CYP3A inducers other than AEDs: (e.g., rifampin, St. John's wort) should be avoided. Carbamazepine, oxcarbazepine and phenytoin increase clearance of Fycompa which decreases Fycompa plasma concentrations and its effectiveness. There is insufficient information to describe dose adjustments that can fully correct for this. Phenobarbital and primidone may also decrease Fycompa concentrations. When these enzyme-inducing AEDs are introduced or withdrawn, patients should be closely monitored since dose adjustment of Fycompa may be necessary. Furthermore, the effectiveness of hormonal contraceptives containing levonorgestrel may decrease with 12 mg once daily dose of Fycompa.

The Drug Enforcement Agency (DEA) has placed FYCOMPA into Schedule III of the Controlled Substance Act with an effective date of January 2, 2014.

DOSAGE

The starting dose is 2 mg once daily at bedtime in patients not on enzyme-inducing AEDs and 4 mg in patients on enzyme-inducing AEDs. Based on clinical response and tolerability, dosage may be increased by a maximum of 2 mg once daily at bedtime in weekly (or for elderly patients, biweekly) increments to a dose of 4 mg to 12 mg once daily at bedtime.

In patients with mild and moderate hepatic impairment, the maximum recommended daily dose is 6 mg and 4 mg once daily at bedtime, respectively. Fycompa is not recommended in patients with severe hepatic or renal impairment (including those requiring hemodialysis).

COST

Drug	Cost/unit	Maximum Cost per 30 Days
Fycompa (perampanel) 2, 4, 6, 8mg tablet	AWP=$11.38-22.75	$1365
Vimpat (lacosamide) 50, 100, 150, 200mg	AWP=$6.74-11.15	$669
levetiracetam 250, 500, 750, 1000mg tablet	MAC=$0.16-0.48	$43
lamotrigine 25, 50, 100, 150, 200mg tablet	MAC=$0.09-0.12	$10
topiramate 25, 50, 100, 200mg tablet	MAC=$0.04-0.17	$10
oxcarbazepine 150, 300, 600mg tablet	MAC=$0.22-0.56	$17
gabapentin 100, 300, 400mg capsule; 600, 800mg tablet	MAC=$0.06-0.41	$37

Maximum cost of alternatives was based on the following dosages per day: Vimpat 400mg, levetiracetam 3000mg, lamotrigine 500mg, topiramate 400mg, oxcarbazepine 600mg, and gabapentin 2400mg.

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Fycompa to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Fycompa [Prescribing Information]. Woodcliff Lake, NJ: Eisai, Inc., November 2012.
- UpToDate, Inc. Pharmacology of antiepileptic drugs. UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated December 11, 2013.
- UpToDate, Inc. Overview of the management of epilepsy in adults. UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated May 13, 2013.