Drug Monograph

Drug/Drug Class:	**Fycompa™ (perampanel) tablet / AMPA glutamate receptor antagonist**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ New Criteria ☐ Revision of Existing Criteria

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 2 mg, 4 mg, 6 mg and 8 mg tablet of Fycompa™ contains 2 mg, 4 mg, 6 mg or 8 mg respectively of perampanel. Eisai Inc., Woodcliff Lake, NJ 07677
Summary of Findings:	Fycompa is a noncompetitive AMPA glutamate receptor antagonist indicated as adjunctive therapy for the treatment of partial-onset seizures in patients with epilepsy aged 12 years and older. Fycompa is the first drug in its class approved for the treatment of partial-onset seizures, providing a new therapeutic drug option for condition.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ Clinical Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1]

Epilepsy and seizures affect nearly 3 million Americans of all ages, and contribute to an estimated $17.6 billion in direct and indirect costs each year. Partial-onset seizures are the most common type of seizure, and occur in approximately 60% of patients with epilepsy.

Dosage Form(s) [2]

Fycompa™ 2mg, 4 mg, 6 mg or 8 mg is available in tablets containing 2 mg, 4 mg, 6 mg, or 8 mg of perampanel respectively.

Manufacturer [2]

Eisai Inc., Woodcliff Lake, NJ 07677

Indication(s) [2]

Fycompa is indicated for patients 12 years of age and older as adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalization.

Clinical Efficacy [2,4-13] (mechanism of action/pharmacology, comparative efficacy)

The precise mechanism by which Fycompa exerts its antiepileptic effects is unknown. Fycompa is a noncompetitive antagonist of the inotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is involved in a number of neurological disorders caused by neuronal over-excitation.

Pharmacokinetics

	FYCOMPA
Protein Binding	95-96%
Volume of Distribution	---
Metabolism	Extensively metabolized via primary oxidation and sequential glucuronidation; oxidative metabolism is mediated by CYP3A4 and/or CYP3A5
Excretion	Feces (48%); Urine (22%)
Half-life	105 hours

FDA approval of Fycompa was based on three global, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation clinical trials comprised of 1480 patients with partial-onset seizures. Results from these trials indicated that adjunctive therapy with Fycompa significantly reduced seizure frequency in patients with partial-onset seizures with or without secondary generalization.

PARTIAL-ONSET SEIZURES

STUDY DESIGN	Three global, randomized, double-blind, placebo-controlled, dose-escalation, parallel-group, clinical trials that evaluated placebo versus multiple Fycompa doses (n=1480)
INCLUSION CRITERIA	Patients aged 12 years and older with partial-onset seizures, with or without secondary generalization, who were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs).
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	All three trials had an initial 6-week run-in period, during which time patients were required to have greater than 5 seizures to qualify for randomization into the trial. The run-in period was followed by a 19-week treatment period, consisting of a 6-week dose titration phase and a 13-week maintenance dose phase. During the dose titration, patients in the Fycompa treatment group initially received 2 mg once daily; subsequent dose increases of 2mg/day occurred in weekly increments until the final target dose for the respective study arm was reached. Patients who experienced intolerable adverse reactions were tapered back down to the previously tolerated dose. The primary outcome measure for each trial was percent change in seizure frequency per 28 days during the treatment period, compared with baseline. Over 85% of patients in the trial were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation. Further, approximately 50% of patients were taking at least one AED known to induce the enzyme CYP3A4 (ie, carbamazepine, oxcarbazepine, or phenytoin), which is critical to the metabolism of Fycompa. CYP3A4 induction significantly decreases the serum concentration of Fycompa, potentially decreasing its efficacy. Patients enrolled in the trial had an average epilepsy duration of approximately 21 years. Median baseline seizure frequency in study subjects ranged from 9.3 to 14.3 seizures/28 day period.
RESULTS	In all three clinical trials, a statistically significant decrease in seizure frequency was observed in patients taking 4 to 12 mg of Fycompa daily. Dose response was apparent at 4 to 8 mg/day, with little additional reduction in seizure frequency noted at doses of 12 mg/day. In Study 1,

	the median percent reduction in seizure frequency from baseline was -13.5% (p=0.0261) and -14.2% (p=0.0158) for patients receiving Fycompa 8 mg/day and 12 mg/day, respectively. In Study 2, the median reduction in seizure frequency from baseline was -19.1% (p=0.0008) and -13.7% (p=0.0105) in the 8mg/day and 12mg/day Fycompa treatment groups, respectively. In Study 3, the median percent reduction in seizure frequency from baseline was -4.4% (p=0.4197), -13.7% (p=0.0026), and -20.1% (p < 0.0001) for patients receiving Fycompa 2 mg/day, 4 mg/day, and 8 mg/day, respectively. Across all 3 trials, 28.5%, 35.3%, and 35% of patients who received Fycompa 4 mg/day, 8 mg/day, and 12 mg/day, respectively, had a 50% or greater reduction in seizure frequency, compared to 19.3% of patients in the placebo group.
SAFETY	The most common adverse reactions were dizziness, drowsiness, fatigue, irritability, falls, upper respiratory tract infections, weight gain, vertigo, ataxia, gait disturbances, balance disorders, anxiety, blurred vision, dysarthria, asthenia, aggression, and hypersomnia.

Contraindications [(2)]

- None

Warnings and Precautions [(2)]

- Serious or life-threatening psychiatric and behavioral adverse reactions have been reported in patients taking perampanel, including aggression, hostility, irritability, anger, and homicidal ideation and/or threats. Monitor for unusual changes in mood, behavior, or personality, especially during dose titration and when taking higher daily doses of perampanel. Dose reduction or drug discontinuation may be necessary.
- Suicidal behavior and ideation may occur in patients taking perampanel. Monitor for depression and suicidal thoughts and/or behaviors.
- Neurological effects are possible when using perampanel. Monitor for dizziness, gait disturbance, somnolence, fatigue, and falls.

Adverse Effects [(2)]

Most common, ≥ 4% Incidence	**Fycompa, 8 or 12 mg/day dose**
	(n=686)
Dizziness	36%
Somnolence	16%
Fatigue	10%
Irritability	9%
Falls	7%
Nausea	7%
Ataxia	5%
Balance disorder	4%
Gait disturbance	4%

Vertigo	4%
Weight gain	4%

Drug Interactions [2]

- Alcohol
- CNS depressants
- CYP3A4 inducers: carbamazepine, oxcabazepine, phenobarbital, phenytoin, primidone, rifampin, St. John's Wort
- Levonorgestrel

Dosage and Administration [2]

Initial dosing of Fycompa depends on an individual's established antiepileptic drug treatment regimen. A 2 mg bedtime starting dose should be utilized in patients who are not taking enzyme-inducing antiepileptic drugs, whereas an initial 4 mg bedtime dose is recommended if patients are taking enzyme-inducing AEDs. Titration should be based on tolerability and clinical response, with a 2 mg/day dose increase occurring no more frequently than weekly intervals to reach a maximum dose of 12 mg/day. Dose increases should occur no more frequently than every 2 weeks in elderly patients and those with pre-existing mild or moderate hepatic impairment. The maximum recommended daily dose is 6 mg for mild hepatic impairment and 4 mg for moderate hepatic impairment.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Perampanel	Fycompa	Eisai, Inc.	2 mg tablets	1 tablet daily	$284.40
			4 mg tablets	1 tablet daily	$568.80
			6 mg tablets	1 tablet daily	$568.80
			8 mg tablets	1 tablet daily	$568.80

*WholesaleAcquisitionCost

Conclusion

Fycompa, a noncompetitive AMPA glutamate receptor antagonist, has demonstrated efficacy as an adjunctive therapy option for the treatment of partial-onset seizures in patients with epilepsy. Fycompa is the first noncompetitive AMPA glutamate receptor antagonist approved for partial-onset seizures, providing a new therapeutic treatment option for this condition. The US Food and Drug Administration has recommended that Fycompa be classified as a scheduled drug by the US Drug Enforcement Administration. Additionally, Fycompa must be dispensed with a patient Medication Guide that provides important safety information and instructions for proper use of the drug.

Recommendation

The Division recommends adding this drug to the current 15 Day Limit fiscal edit and Psychotropic Polypharmacy clinical edit.

References

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Prepared by: Ashley Renée Miller, PharmD Candidate

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