Perampanel (Fycompa)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Perampanel is a highly selective, non-competitive AMPA receptor antagonist that blocks excessive excitatory neuronal signaling, preventing the opening of ion channels and ultimately reducing action potential propagation. This pathway is believed to play a critical role in seizure propagation.
Indication(s) Under Review in this document (may include off label)	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
Dosage Form(s) Under Review	Oral tablet
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C

Executive Summary	
Efficacy	• Perampanel resulted in a statistically significant reduction of seizure frequency with respect to the 50% responder rate in patients with partial onset epilepsy. Perampanel is well tolerated at 4 mg and reasonably tolerated at 8 mg and 12 mg. • A meta-analysis of 5 published clinical trials demonstrated the 50 % responder rates were significantly greater in patients receiving 4, 8 and 12 mg perampanel versus placebo, with risk ratios of 1.54 (95 % CI 1.11–2.13), 1.80 (95 % CI 1.38–2.35) and 1.72 (95 % CI 1.17–2.52), respectively. There was no statistical evidence of a difference in seizure freedom between 8 or 12 mg perampanel vs. placebo • A post hoc analysis of the Phase III trials demonstrated the patients taking 1 antiepileptic(AED) drug at baseline had a significantly higher 50% responder rate compared to those taking 3 AEDs at baseline($P < 0.02$). • At higher perampanel doses, in general, more patients had large reductions in seizure frequency, and more patients were free from secondarily generalized seizures with perampanel 12 mg. Seizure-free rates ranged from 15.3% to 35.7% in the perampanel-treated groups. .
Safety	• Perampanel is the only antiepileptic with a black box warning for serious psychiatric and behavioral reactions. • Common adverse effects include weight gain, fatigue and nausea. • Neurologic adverse effects include dizziness, somnolence, irritability, gait disturbance, falls, aggression and mood alteration
Potential Impact	• Perampanel is a first in class non-competitive antagonist of the a-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid (AMPA) glutamate receptor. AMPA receptors are found on the excitatory synapses in the central nervous system. Non-competitive antagonism means that inhibitory effects are less likely to be overwhelmed during seizures. • Perampanel displays good oral bioavailability (100%), is rapidly absorbed

(Tmax, 0.25–2.0 h) and demonstrates no sign of significant first-pass metabolism. It demonstrates linear pharmacokinetics in healthy individuals at doses of 2–12 mg/day and is extensively metabolized (98%), primarily by CYP3A4. This can impact therapy when an enzyme inducing AED is used concomitantly. The advantage of once daily dosing and predictable blood levels is significant in an epilepsy population, especially on concomitant therapies.

- In pooled analysis of the Phase III trials, perampanel demonstrated the median percent change in secondary generalized seizure frequency was 48.6%, 62.9%, and 53.3% with perampanel 4, 8, and 12 mg, respectively, vs 19.4% with placebo. As well as seizure freedom ranging from 15.3%- 35.7% of patients.
- The significant lowering in the secondarily generalized seizure rate is important in a difficult to treat population on multiple AED. There is paucity of evidence in this patient population with second and third generation AEDs. The robust evidence for perampanel defines a population is likely to show clinical benefit with this agent.

Background

Purpose for review

Issues to be determined:

✔ Is there a need for therapeutic alternatives to be used as therapy in patients with epilepsy?
✔ Does perampanel offer advantages to currently available therapies?
✔ Does perampanel offer advantages over current VANF agents?
✔ What safety issues need to be considered?
✔ Does perampanel have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations
Carbamazepine	Liver dysfunction, hyponatremia, rash, agranulocytosis, Stevens Johnson Syndrome
Lacosamide	Not to be used with AV conduction block
Lamotrigine	Slow titration to avoid rash. Do not use in tremor and myoclonus
Levetiracetam	May worsen major depressive disorder. PTSD, anxiety, thought disorders
Oxcarbazepine	Rash, hyponatremia

Efficacy (FDA Approved Indications)

Literature Search Summary

MEDLINE and EMBASE were systematically searched using search terms perampanel, Fycompa, epilepsy, refractory epilepsy, seizure treatment, epilepsy treatment and refractory seizures for randomized controlled trials published from 1980 through February 1, 2016. Additionally, articles relating to pharmacology, pharmacokinetics, tolerability and interactions were examined for inclusion. Published abstracts and websites of the Food and Drug Administration and European Medication Agency were reviewed for additional relevant information. The search was limited to studies performed in humans, in adults and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy
Currently available evidence (Please refer the reader to Appendix A for interpretation) is rated at a high level.

The results of Phase II studies evaluating the tolerability and safety of dose-escalation of perampanel in patients with refractory partial seizures were reported by Krauss, et al.[3] Study 206 investigated the safety and tolerability of perampanel titrated up to 4 mg daily as a once-daily versus twice-daily administration compared to placebo. Eighty-two percent of patients in all 3 groups tolerated the maximum dose of 4 mg per day. The 50% responder rate (defined as the percentage of subjects who experienced ≥50% reduction in seizure frequency during the maintenance phase compared to baseline) was 33% for once-daily dosing of perampanel and 28% for twice-daily dosing. The median reduction in seizure frequency was 25.7% in the perampanel groups and 19.5% in the placebo group (P=.43). Study 208 examined the safety and tolerability of perampanel 12 mg daily. Perampanel was initiated at 2 mg daily, and titrated by 2 mg every 2 weeks to reach the maintenance dose of 12 mg daily. Subjects remained on the maintenance dose for 4 weeks. Based on the Kaplan-Meier analysis, the probabilities of tolerating 8 mg, 10 mg, and 12 mg perampanel were 0.55, 0.48, and 0.44, respectively, compared with 0.88 for placebo The median percent change in seizure frequency was -39.6% in the perampanel-treated group and +2.1% in the placebo group. Fifty percent responder rates were 22.2% for perampanel and 39.5% for placebo.

An open-label trial evaluated the long-term tolerability, safety, and efficacy of high-dose (12 mg daily) perampanel over 4 years in patients with refractory partial-onset seizures.[4] The median percent change in seizure frequency per 28 days over 1, 2, 3, or 4 years of perampanel exposure was -43.7%, -52.0%, -49.7%, and -48.4%, respectively, with an overall -39.4% change during the maintenance period.15 In addition, the 50% responder rate over 1, 2, 3, or 4 years was 43.8%, 51.5%, 49.0%, and 50.0%, respectively, and overall 45.8% during the maintenance period. Of the 131 subjects with complex partial seizures, 15 subjects (10.9% overall) reported ≥75% reduction in seizure frequency, with 4 of those subjects (2.9% overall) reporting 100% reduction.

The efficacy of perampanel 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 304, 305, and 306) in adult and adolescent patients . 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).

The first completed phase 3 trial, Study 306,[5] assessed the safety and efficacy of adjunctive perampanel 2 mg, 4 mg, and 8 mg daily in subjects with epilepsy with refractory partial-onset seizures who were uncontrolled on up to 3 concomitant AEDs. Immediately prior to randomization, eligible subjects were required to have experienced at least 5 partial seizures without a 25-day seizure-free interval over 6 weeks and have taken up to 3 different AEDs for 3 weeks. Subjects were randomly assigned (1:1:1:1) to placebo, 2 mg, 4 mg, or 8 mg perampanel daily. Perampanel was initiated at 2 mg daily, titrated up every 2 weeks by 2 mg daily, and maintained for 13 weeks at the assigned dose. The average percentage of subjects taking 1 concomitant AED was 14.7%, and 85.3% were taking either 2 or 3 AEDs. The median percent change in seizure frequency per 28 days for placebo and perampanel 2 mg, 4 mg, and 8 mg daily was -10.7%, -13.6%, -23.3%, and -30.8%, respectively, and 50% responder rates were 17.9%, 20.6%, 28.5%, and 34.9%, respectively. Patients in both the perampanel 4-mg and perampanel 8-mg groups demonstrated statistically significant decreases in seizure frequency (P=.0026, P<.0001, respectively) and improvements in 50% responder rate (P=.0132, P=.0003, respectively).There was no statistically significant difference between perampanel 2 mg daily and placebo (P=.420).

The safety and efficacy of perampanel 8 mg and 12 mg daily in comparison to placebo was investigated with Study 305.[6] Eligible subjects were randomly assigned (1:1:1) to placebo, perampanel 8 mg, or perampanel 12 mg. Dosing was initiated at 2 mg daily and titrated up by 2 mg daily at 2-week intervals until the desired dose was achieved and sustained during the 13-week maintenance period. Of the 386 randomized subjects, 321 completed the study, 88.2% from the placebo group, 83.7% from the 8-mg perampanel group, and 76.9% from the 12-mg perampanel group. A 50% responder rate was achieved in 14.7% in the placebo group, compared with 33.3% for 8-mg perampanel-treated patients (P=.002) and 33.9% for 12-mg perampanel-treated patients (P<.001). Median percent change in seizure frequency per 28 days over the entire duration of the study was -30.5% for 8 mg perampanel (P<.001 based on rank ANCOVA test, P=.001 based on log transformation ANCOVA test) and -17.6% for 12 mg perampanel (P=.011 based on rank ANCOVA test, P=.025 based on log transformation ANCOVA test) compared to -9.7% for placebo.

Study 304[7] was identical in study design and protocol to Study 305, except that it was conducted in different geographical locations, including Argentina, Canada, Chile, and Mexico. Three hundred eighty-eight subjects were randomly assigned (1:1:1) to placebo, perampanel 8 mg, or perampanel 12 mg. Median percent change in seizure frequency per 28 days over the entire duration of the study was -21.0% for placebo and -25.3% (P=.0261) for perampanel 8 mg and -34.5% (P=.0158) for perampanel 12 mg.18 Responder rates were 37.6% (P=.0760) for perampanel 8 mg and 36.1% (P=.0914) for perampanel 12 mg compared to -17.9% for placebo.18

Extension Study 307[8] examined the long-term safety and tolerability of high-dose perampanel as adjunctive therapy in patients with refractory partial-onset seizures who completed Study 304, 305, or 306. Within 14 days of completion of the double-blind study, subjects began at the last dose received and titrated by 2 mg every 2 weeks up to 12 mg. An open-label maintenance period was planned for 256 weeks. Of the 1,264 subjects who completed 1 of the 3 phase 3 trials, 1,218 (96.4%) continued to the extension study and 1,186 completed Study 307. In addition to the study medication, subjects used 1 AED (13.4%), 2 AEDs (50.3%) or 3 AEDs (36.3%), with most subjects using carbamazepine (33.7%), valproic acid (33.6%), lamotrigine (31.5%), and/or levetiracetam (29.0%). Seizure frequency continued to decrease over the first 26 weeks, then plateaued for the remainder of the extension study. The median seizure frequency per 28 days was 11.2.The median percent change in seizure frequency per 28 days over the entire duration of the study was -47.2% in patients who received treatment for >1 year, and -56.0% in those who received treatment for >2 years. The 50% responder rate after 1 year of treatment was 47.6%, and 63.2% after 2 years.19 Seven percent of subjects reported a 1-year seizure-free period after 12 months.

There have been several post hoc analysis conducted on the Phase III trials. Gidal, et al;[14] found that perampanel dosed at 8 and 12 mg, demonstrated a higher treatment response in patients who were not receiving concomitant antiseizure medications which were CYP3A4 inducers. Additionally, the treatment effect of perampanel r was dose dependent. The adverse effect profile displayed the same dose dependent response.

There have been several reports investigating a pooled data set of the Phase III trials.[15-18] These reports have all demonstrated the robust efficacy of perampanel in regards to responder rate, seizure free periods and decreases in seizure frequency in both complex partial seizures as well as secondarily generalized seizures. The influence of concomitant AED therapy, with patients on 1 AED demonstrating a more significant impact on responder rate and seizure frequency in comparison to 3 AED, is likely related to the duration of seizure history as well a lower number of baseline seizures than the 3 AED group. A systematic review and meta-analysis by Hsu et. al;[19] confirmed a statistically significant reduction in seizure frequency in respect to the 50% responder rate. When the different dosages of perampanel are compared using a forest plot, it appears that the dose dependent response to perampanel plateaus at 8 mg as the 12 mg dose did not offer any significant increase in responder rate.

Potential Off-Label Use

None noted

Safety [10-13]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• 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 perampanel. • 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 taking perampanel should be advised to avoid the use of alcohol, as it may exacerbate these effects. • Closely monitor patients particularly during the titration period and at higher doses.

Contraindications	• None
Warnings/Precautions	• Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behavior • Neurologic Effects: Monitor for dizziness, gait disturbance, somnolence, and fatigue • Patients should use caution when driving or operating machinery • Falls: Monitor for falls and injuries • Withdrawal of Antiepileptic Drugs: In patients with epilepsy, there may be an increase in seizure frequency

Adverse Reactions

Common adverse reactions	The most common dose-related adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥4% and occurring at least 1% higher than the placebo group) 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.
Death/Serious adverse reactions	No deaths reported
Discontinuations due to adverse reactions	In controlled clinical trials, the rate of discontinuation as a result of an adverse reaction was 3%, 8%, and 19% in patients randomized to receive perampanel at the recommended doses of 4 mg, 8 mg, and 12 mg per day, respectively, and 5% in patients randomized to receive placebo. The adverse reactions most commonly leading to discontinuation (≥1% in the 8 mg or 12 mg perampanel group and greater than placebo) were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria.

Perampanel is a C-III substance. The human abuse potential of single oral doses of perampanel (8 mg, 24 mg, and 36 mg) were compared to alprazolam C-IV (1.5 mg and 3 mg), and oral ketamine C-III (100 mg) in a study with recreational polydrug users. Supra-therapeutic doses of 24 and 36 mg produced responses for "Euphoria" that were similar to ketamine 100 mg and alprazolam 3 mg. "Drug Liking", "Overall Drug Liking", and "Take Drug Again" for perampanel were each statistically lower than ketamine 100mg. In addition, for "Bad Drug Effects", 24 mg and 36 mg produced responses significantly higher than ketamine 100mg. For "Sedation," perampanel 24 mg and 36 mg produced responses similar to alprazolam 3 mg and higher than ketamine100 mg.

Drug Interactions[14]

Strong CYP3A inducers other than AEDs: (e.g., rifampin, St. John's wort) should be avoided. Carbamazepine, oxcarbazepine and phenytoin increase clearance of perampanel which decreases 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 perampanel concentrations. When these enzyme-inducing AEDs are introduced or withdrawn, patients should be closely monitored since dose adjustment of perampanel may be necessary. Furthermore, the effectiveness of hormonal contraceptives containing levonorgestrel may decrease with 12 mg once daily dose of perampanel.

Risk Evaluation

As of February 15, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC

Dosing and Administration

Dosing in the absence of enzyme-inducing antiepileptic drugs (AEDs)

- Starting dose: 2 mg once daily orally at bedtime
- May increase dose based on clinical response and tolerability by increments of 2 mg once daily no more frequently than at weekly intervals
- Recommended maintenance dose: Partial-Onset Seizures – 8 to 12 mg once daily at bedtime; Primary Generalized Tonic-Clonic Seizures – 8 mg once daily at bedtime

Dosing in the presence of enzyme-inducing antiepileptic drugs (AEDs)

- Enzyme-inducing AEDs, including phenytoin, carbamazepine, and oxcarbazepine, cause a 50-67% reduction in perampanel plasma levels
- In patients receiving concomitant enzyme-inducing AEDs, the recommended starting dosage of perampanel is 4 mg once daily taken orally at bedtime.
- Increase dosage by increments of 2 mg once daily no more frequently than at weekly intervals. A maintenance dose has not been established in clinical trials. The highest dose studied in patients on concomitant enzyme-inducing AEDs was 12 mg once daily

Special Populations (Adults)

	Comments
Elderly[25]	• increase dosage no more frequently than every 2 weeks during titration • Because the risk of falls, dizziness, and fatigue were greater in the elderly, careful titration of perampanel in patients aged ≥ 65 years is suggested, especially at higher doses, where balancing tolerability and clinical response is necessary.
Pregnancy	• Perampanel is classified as a pregnancy category C.
Lactation	• There are no data on the presence of perampanel in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Perampanel and/or its metabolites are present in rat milk, and are detected at concentrations higher than that in maternal plasma.
Renal Impairment	• Perampanel can be used in patients with moderate renal impairment with close monitoring. A slower titration may be considered, based on clinical response and tolerability. It is not recommended in patients with severe renal impairment or patients undergoing hemodialysis.
Hepatic Impairment	• In patients with mild and moderate hepatic impairment, the starting dose of perampanel is 2 mg once daily. Increase dosage by increments of 2 mg once daily no more frequently than every 2 weeks. The maximum recommended daily dose is 6 mg for patients with mild hepatic impairment and 4 mg for patients with moderate hepatic impairment. Perampanel is not recommended for use in patients with severe hepatic impairment.

Projected Place in Therapy

Perampanel 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).

Perampanel is the only product with a boxed warning for hostility, aggression and homicidal ideation. It's long duration of action can prolong adverse effects of sedation, headache, and dizziness. Perampanel has been associated with gait disturbances and an increased risk for falls. This may hamper the utility of this agent in an elderly population. From the evidence available, perampanel can be considered for combination therapy in refractory patients with secondary generalized seizures, or exclusively for focal seizures as a second- or third-line agent. There are trials in progress which will help define the utility of perampanel in tonic clonic seizures and idiopathic generalized epilepsy.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.