Brand Name: Fycompa

Generic Name: perampanel

Manufacturer: [3] Eisai Inc.

Drug Class:[1,2] AMPA Glutamate Receptor Antagonist; Anticonvulsant, Miscellaneous

Uses:

Labeled Uses:[1,2,4] Adjunctive treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy ages 12 years and older

Unlabeled Uses:[1,2,4] None

Mechanism of Action:[3]

The exact mechanism is not completely known. Perampanel is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is an excitatory neurotransmitter in the CNS and is involved in many neurological disorders.

Pharmacokinetics: [2,3,8]

Absorption: Rapid and complete after oral administration

Half-life	105 hours
Tmax	0.5-2.5 hours
Vd	77L (51-105)
Clearance	12mL/min
Protein binding	95-96% to albumin and alpha 1-acid glycoprotein
Bioavailability	116%

Metabolism: Primarily metabolized by oxidation mediated by CYP3A4/5 and sequential glucuronidation.

Elimination: Following a single dose, 22% was recovered in the urine and 48% was recovered in the feces, mainly as a mixture of oxidative and conjugated metabolites.

Efficacy:

French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, Kumar D, Rogawski MA. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012 Aug 7;79(6):589-96.

Study Design: Multicenter, multinational, randomized, double-blind, placebo-controlled design study

Description of Study: *Methods:* Of the 534 patients screened, 388 were randomized and received once daily treatment of either placebo (n=121), perampanel 8mg (n=133), or perampanel 12mg (n=134) in addition to their current antiepileptic drugs (AED). This study utilized a 19-week treatment phase, consisting of 6-week titration and 13-week maintenance periods. Patients' medications were titrated in 2mg increments weekly up to the randomized dose. The efficacy assessments included seizure counts from patients' diaries, Clinical and Patient Global Impression of Change (CGIC/PGIC), and the Quality of Life in Epilepsy questionnaire (QOLIE-31-P). Safety assessments were also conducted. Patients were withdrawn from the trial if they could not tolerate 2mg of perampanel or placebo at the end of the titration phase. *Outcome Results:* The median percent change in seizure frequency was -26.3% (p=0.0261), -34.5% (p=0.0158), and -21.0% for 8mg, 12mg, and placebo respectively. These results were statistically significant. Fifty percent responder rates were 37.6% for 8mg (p=0.0760), 36.1% for 12mg (p=0.0914) and 26.4% for placebo. The CGIC and PGIC showed "much" or "very much" improvement with perampanel treatment. The QOLIE-31-P responses showed similar changes in quality of life between all groups. Most frequent treatment emergent adverse events(TEAEs) associated with perampanel and leading to discontinuation included: dizziness, ataxia, aggression, vertigo, dysarthria, somnolence, and blurred vision. Mean changes in laboratory values, ECGs, vital signs, and physical or neurologic examinations were not clinically significant.

Limitations: This study was funded by Eisai Inc., the manufacturer of this drug. Several authors are affiliated with or employed by the manufacturer. This allows the possibility of bias in this study. The duration was too short to see any long-term effects. Another limitation is that perampanel was only studied in people over the age of 12 with highly treatment-resistant seizures; therefore, the findings can't be extrapolated to children or for use as monotherapy.

Conclusion: This study shows that perampanel, used as adjunctive therapy for highly treatment-resistant partial-onset seizures, can reduce the frequency of those seizures when given doses of 8mg or 12mg once daily. These two doses showed significantly reduced frequency of seizures compared to placebo. The majority of TEAEs were mild or moderate for both doses. The TEAEs occurred more frequently while titrating the medication than in the maintenance period, suggesting they were related to the fixed titration schedule.

Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012 May 1;78(18):1408-15.

Study Design: Multicenter, multinational, double-blind, placebo-controlled, randomized study design

Description of the Study: *Methods:* Of the 878 patients screened, 705 were randomized and received once daily treatment of either placebo (n=184), perampanel 2mg (n=180), perampanel 4mg (n=172), or perampanel 8mg (n=169) in addition to their current antiepileptic drugs (AED). The study used a 19-week treatment phase, consisting of 6-week titration and 13-week maintenance periods. Patients' medications were titrated in 2mg increments weekly up to the

randomized dose. The efficacy assessments included seizure counts from the patients' diaries, Clinical and Patient Global Impression of Change, and the Quality of Life in Epilepsy questionnaire. Safety assessments were also included. Patients not tolerating their drug dose by the end of the titration phase were withdrawn from the study. *Outcome Results:* The median percent change in seizure frequency was -10.7% for placebo, -13.6% for 2mg/day (p=0.420), -23.3% for 4mg/day (p=0.003), and -30.8% for 8mg/day (p=<0.001). The CGIC and PGIC showed much or very much improvement with perampanel. The fifty percent responder rates were 17.9% for placebo, 20.6% for 2mg/day, 28.5% for 4mg/day (p=0.013), and 34.9% for 8mg/day (p=<0.001). TEAEs were mostly mild to moderate in severity. The most common adverse events that required discontinuation were dizziness, convulsion, fatigue, and vertigo. The mean changes in laboratory values, vital signs, and ECGs were not clinically significant for any of the groups.

Limitations: This study was funded by Eisai Inc., the manufacturer of this drug. Several authors are affiliated with or employed by the manufacturer. This allows the possibility of bias in this study. The duration was too short to show any long-term effects. Another limitation is that perampanel was only studied in people over the age of 12 with highly treatment-resistant seizures; therefore, the findings can't be extrapolated to children or for use as monotherapy.

Conclusion: This study shows that perampanel, used as adjunctive therapy for partial-onset seizures, with or without secondary generalization is safe and effective at doses of 4mg/day or 8mg/day. Doses of 2mg/day were not seen to show any statistical significance compared to placebo; therefore, this study showed the minimal effective dose to be 4mg/day.

Krauss GL, Bar M, Biton V, Klapper JA, Rektor I, Vaiciene-Magistris N, et al. Tolerability and safety of perampanel: two randomized dose-escalation studies. ActaNeurolScand: 2012: 125: 8–15.

Study Design: Study 206 and 208 were both multicenter, multinational, randomized, double-blind, placebo-controlled, dose-escalation, parallel-group studies

Description of the Study: *Methods for Study 206:* There were 153 patients randomized to either placebo (n=51), perampanel twice daily (n=51) or perampanel once daily (n=51). The study had 4 phases: baseline, titration, maintenance, and follow-up. The 8-week titration phase started with a dose of 1mg/day (0.5 mg/twice daily or 1mg/day). Doses were then titrated in 1mg increments every 2 weeks to a maximum of 4mg/day (2 mg/twice daily or 4mg/day). Tolerability and safety was assessed in the study. Patients were considered to not have tolerated the dose if discontinuation of the study occurred due to an AE or if the dose was titrated down. *Methods for Study 208:* There were 48 patients randomized to either placebo (n=10) or perampanel 2mg/day (n=38). The study had 4 phases: baseline, titration, maintenance, and follow-up. The 12-week titration phase started all perampanel treated patients on 2mg/day and titrated by 2mg/day every 2 weeks to a maximum of 12mg/day. Tolerability and safety was assessed in this study. Patients were considered to not have tolerated the dose if discontinuation of the study occurred due to an AE or if the dose was down-titrated. *Outcome Results for Study 206:* Of the 153 patients, 138 completed this study. The highest dose tested was 4mg/day and was tolerated by the majority of the patients. The most common AE were dizziness, headache, and somnolence and were mostly mild to moderate. There were no clinically significant differences between placebo and perampanel in clinical laboratory values, ECG, or any safety variable. The tolerability and safety data showed

the majority of patients tolerated 4mg/day, and the maximum tolerated dose was not reached. The responder rate was 30.7% with perampanel and 21.6% with placebo (p=0.19). In the perampanel twice daily and once daily groups, responder rate was 28.0% and 33% respectively. The median reduction in seizure frequency was 25.7% in all perampanel treated patients and 19.5% in the placebo group (p=0.43). *Outcome Results for Study 208:* Of the 48 patients, 42 of them completed this study. This study looked at higher doses of perampanel (8mg, 10mg, and 12mg/day). Of the 28 patients who took 8mg/day, 18 remained on that dose afterwards. Of the 16 patients who took 10mg/day, 14 remained on that dose, and of the 12 who took 12mg/day, 11 remained on that dose. The most common AEs in doses greater than 6mg/day were dizziness, somnolence, and headache. Other AEs that were seen at doses greater than 6mg/day were nausea, gait disturbance, dysarthria, and insomnia. The majority of the AEs were mild to moderate. There were no differences in perampanel compared to placebo in any other safety assessments. The responder rates in the overall treatment phase were 22% and 39.5% in the placebo and perampanel groups, respectively. The median reduction in seizure frequency with perampanel was 39.6%; a median increase of 2.1% was seen in the placebo group.

Limitations: The studies were both funded by Eisai Inc., the manufacturer of perampanel. Several authors are affiliated with or employed by the manufacturer. This allows the possibility of bias in these studies. These studies included 18-70 year olds weight more than 40kg; therefore, these results cannot be extrapolated to the older population or those with a very low weight. The small sample size for the higher doses may not be adequate to show true results. The duration of these studies may be a limitation for assessing the safety and tolerability.

Conclusion: In study 206, it was shown that the majority of people can tolerate doses up to 4mg/day of perampanel. They also reported that the maximum tolerated dose was greater than 4mg/day, suggesting that higher doses need to be studied in order to compare true efficacy versus placebo. There were no differences in patients' abilities to tolerate either twice a day or once a day dosing. Also, the main AEs were mild to moderate. In study 208, it was shown that most patients could tolerate doses of 6mg/day or more. They showed that about 44% of patients could tolerate the highest tested dose of 12mg/day. Due to the small sample size and the wide CI, this dose of perampanel needs to be investigated further. These studies reported that perampanel can be used as adjunctive therapy in adults 18-70 years old weighing 40kg or more for partial-onset seizures with or without secondary generalization. These studies proved the safety and efficacy at lower doses and that the maximum tolerated dose was greater than 4mg/day. Due to the small numbers of patients in each group, statistical significance for efficacy could not be concluded in study 208.

Contraindications: [1,2,3,4] None

Precautions: [1,2,3,4]

Neuropsychiatric disorders (Black box warning): Serious neuropsychiatric events (including aggression, anger, homicidal thoughts, hostility, and irritability) have been reported in the first 6 weeks of therapy. Patients should be monitored closely. Adjust dose or discontinue use if severe or worsening symptoms occur.

Suicidal ideation: Many antiepileptics have an increased risk of suicidal thoughts/behavior observed within 1 week of initiation and continued throughout treatment. Monitor patients for changes in behavior that might resemble depression or suicidal thoughts.

CNS effects: Dizziness, fatigue, gait disturbances, and somnolence may occur during therapy. Counsel patients about performing tasks which require alertness.

Hepatic impairment: Not recommended for patients with severe impairment; dosage adjustments recommended for mild-to-moderate impairment.

Renal impairment: Not recommended for patients with severe impairment or on hemodialysis; use caution in patients with moderate impairment.

Fall risk: Use with caution in patients who are at risk of falls.

Withdrawal: Therapy should be withdrawn gradually (over 1 week or more) to avoid increasing seizure frequency.

Adverse Effects:[2,3,4]

Occurring in >10% of patients:

Central nervous system

- Dizziness (16% to 43%)
- Somnolence (9% to 18%)
- Headache (13%)
- Fatigue (8% to 12%)
- Irritability (4% to 12%)

Occurring in 1% to 10%:

Cardiovascular

- Peripheral edema (2%)

Central nervous system

- Ataxia (1% to 8%)
- Vertigo (3% to 5%)
- Balance impaired (≤5%)
- Gait disturbance (4%)
- Anxiety (2% to 4%)
- Aggression (2% to 3%)
- Hypersomnia (1% to 3%)
- Anger (≤3%)
- Hypoesthesia (≤3%)
- Confusion (2%)
- Coordination impaired (≤2%)
- Euphoria (≤2%)
- Memory impaired (≤2%)
- Mood changes (1% to 2%)

Dermatologic

- Bruising (≤2%)
- Skin laceration (≤2%)

Endocrine & metabolic
- Hyponatremia (≤2%)

Gastrointestinal
- Weight gain (4% to 9%)
- Nausea (6% to 8%)
- Vomiting (4%)
- Constipation (3%)

Neuromuscular & skeletal
- Falling (5% to 10%)
- Back pain (5%)
- Dysarthria (1% to 4%)
- Myalgia (3%)
- Arthralgia (≤3%)
- Limb pain (≤3%)
- Limb injury (2%)
- Musculoskeletal pain (2%)
- Weakness (2%)
- Paresthesia (≤2%)

Ocular
- Blurred vision (3% to 4%)
- Diplopia (3%)

Respiratory
- Cough (4%)
- Upper respiratory tract infection (4%)
- Oropharyngeal pain (2%)

Miscellaneous
- Head injury (3%)

Drug Interactions: [2,3]

Alcohol

Perampanel may enhance the CNS depressant effect of alcohol. Alcohol may also worsen the behavioral/psychiatric effects of perampanel.

Aripiprazole

May decrease the serum concentration of aripiprazole.

Axitinib

May decrease the serum concentration of axitinib.

Carbamazepine, oxcarbazepine, phenytoin, fosphenytoin

May increase clearance of perampanel and decrease perampanel's effectiveness.

CNS Depressants

Perampanel may enhance the CNS depressant effect of CNS depressants.

Contraceptives

12 mg once daily dose may decrease the effectiveness of hormonal contraceptives containing levonorgestrel.

Deferasirox

May decrease the serum concentration of CYP3A4 substrates.

Ketorolac

May diminish the therapeutic effect of anticonvulsants.

Mefloquine

May decrease the serum concentration of anticonvulsants.

Other Strong CYP3A Inducers (e.g. rifampin, St. John's Wort)

May decrease perampanel concentrations.

Phenobarbital, primidone

May decrease perampanel concentrations.

Saxagliptin

May decrease the serum concentration of saxagliptin.

Selective Serotonin Reuptake Inhibitors

CNS depressants may enhance the adverse effects of selective serotonin reuptake inhibitors.

Dosing/Administration: [1,2,3,4]

Adult

Patients not receiving enzyme-inducing AED regimens:

Initial: 2mg orally once daily at bedtime
Titration: Increase daily dose by 2mg at weekly intervals as tolerated
Maintenance: 8-12mg once daily at bedtime

Patients receiving enzyme-inducing AED regimens:

Initial: 4mg orally once daily at bedtime
Titration: Increase daily dose by 2mg at weekly intervals as tolerated
Maintenance: 8-12mg once daily at bedtime

Geriatric

Refer to adult dosing; increase dose no more frequently than every 2 weeks

Pediatric

Not for use in children < 12 years of age
Children 12 years and older, refer to adult dosing

Renal impairment

Mild: No dosage adjustment necessary
Moderate: No dosage adjustment necessary; monitor closely, consider slower titration
Severe: Not recommended; has not been studied
Hemodialysis: Not recommended; has not been studied

Hepatic impairment

Mild: Initial 2mg once daily; may increase daily dose by 2mg every 2 weeks as tolerated. Maximum 6mg once daily

Moderate: Initial 2mg once daily; may increase daily dose by 2mg every 2 weeks as Tolerated. Maximum 4mg once daily

Severe: Not recommended; has not been studied

Use in Special Circumstances: [1,2,3,4]

Substance abuse: Perampanel is a controlled substance which can cause physical and psychological dependence and can produce euphoric symptoms at doses of 24 or 36mg. Use caution in patients with known, suspected, or a history of substance abuse.

Pregnancy: Pregnancy category C; adverse events were seen in animal reproduction studies at doses that are equivalent to human doses. Contraceptives containing levonorgestrel are less effective during therapy; other nonhormonal forms of contraception are recommended.

Lactation: Excretion in breast milk is unknown; use caution.

Pediatric: Not for use in children less than 12 years of age.

Conclusion:

Perampanel is effective as adjunctive therapy in patients 12 years of age or older for uncontrolled partial-onset seizures with or without secondary generalization and are taking 1-3 approved concomitant antiepileptic drugs. Studies showed that targeting glutamatergic neurotransmission using AMPA-receptor antagonism is a good approach to seizure treatment. Comparing the results of clinical trials of perampanel with clinical trials of other newly approved AEDs, perampanel was similar to the other medications when showing the magnitude of seizure reduction; however, true head to head studies are needed to confirm this. The side effects and adverse events seen with perampanel were mostly mild to moderate. This medication was studied in combination with other antiepileptic drugs; therefore, it is not shown to control seizures as monotherapy. Perampanel must be used in combination with 1-3 other approved concomitant antiepileptic drugs.

Recommended References:

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8. Yang X, Lee JY, Bhattaram V, Wu TC, Mehta MU. Clinical Pharmacology Review. Fycompa. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM332052.pdf.Accessed January 18, 2013.

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