

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202834Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: October 21, 2012

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 202834

SUBJECT: Recommendations for Action on NDA 202834, for the use of Fycompa (perampanel) Tablets as adjunctive treatment for patients 12 years of age and older with partial onset seizures

NDA 202834, for the use of Fycompa (perampanel) Tablets as adjunctive treatment for patients 12 years of age and older with partial onset seizures, was submitted by Eisai Co., on 12/22/11. Perampanel is a non-competitive alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic (AMPA) receptor antagonist, the first in its pharmacologic class to be proposed as an anticonvulsant. The application contains the results of three randomized controlled trials, as well as open-label safety data and non-clinical, chemistry and manufacturing control (CMC), and clinical pharmacology data.

The application has been reviewed by Dr. Martin Rusinowitz, neurology medical officer, Dr. Mary Doi, safety reviewer, Dr. Sally Yasuda, safety team leader, Dr. Ququan Liu, statistician, Drs. Xinning Yang and Joo-Yeon Lee, Office of Clinical Pharmacology, Dr. Christopher Toscano, pharmacology reviewer, Dr. Lois Freed, pharmacology team leader, Dr. Lyudmila Soldatova, Office of New Drug Quality Assessment, Dr. Alicja Lerner, Controlled Substance Staff (CSS), Shawna Hutchins, Division of Medical Policy Programs, Dr. Kendra Worthy, Division of Risk Management, Dr. Antoine El-Hage, Office of Scientific Investigations (OSI), Drs. Sripal R. Mada and Niraj Mehta, OSI Bioequivalence and GLF Compliance, Dr. Tien-Mien Chen, ONDQA Biopharmaceutics, Dr. Loretta Holmes, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Monica L. Fiszman, QT Interdisciplinary Review Team, Dr. Ling Chen, statistician, Special Project Team (CSS), Dr. Wei Ye, Method Validation, Dr. Virginia Elgin, Pediatric and Maternal Health Staff, the Executive Committee of the Carcinogenicity Assessment Committee (CAC), and Dr. Norman Hershkowitz, neurology team leader and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved. Below, I will briefly review the relevant data and offer the division's recommendation for action on the NDA.

Effectiveness

As noted above, the sponsor has submitted the results of three randomized controlled trials that they believe establish substantial evidence of effectiveness for perampanel as adjunctive therapy for partial seizures in patients 12 years of

age and older. These studies are all of similar design, and are described below.

Study 304

This was a multiple fixed dose, double blind, multi-center study in which patients with partial seizures were randomized to receive target doses of perampanel of either 8 or 12 mg/day, once daily, or placebo. Treatment was to be initiated (after a prospective 6 week baseline phase) at 2 mg/day in all patients, with the dose increased by 2 mg/day every week; therefore, this titration phase lasted 6 weeks (including in those patients randomized to the non-12 mg/day arms). This phase was followed by a 13 week maintenance phase. The daily dose could be lowered if not tolerated, though attempts were to be made to increase the dose to the target dose.

Patients were to be receiving from 1-3 background anti-epileptic drugs (AED), only one of which could be an enzyme-inducing drug (EIAEDS: carbamazepine, Phenobarbital, phenytoin, oxcarbazepine, primidone). EIAEDs increase the clearance of perampanel 2-3 fold.

The primary outcome was the Percent Change from Baseline in 28 day partial seizure frequency for the 13 week Maintenance phase. Secondary outcomes included:

- 1) Percent Change from baseline in 28 day seizure frequency of complex partial seizures
- 2) Responder Rate, defined as a decrease in seizure frequency of at least 50% compared to the baseline frequency
- 3) Dose response

For the primary analysis, the baseline and maintenance seizure frequencies were rank transformed (separately) and analyzed with an analysis of covariance (ANCOVA) with treatment and pooled countries as factors, and baseline seizure frequency as a covariate (the strategy for pooling countries is described in detail by Dr. Liu). In this study (as well as in Study 305), the 8 mg/day dose group was first compared to placebo; if this comparison was statistically significant at alpha 0.05, then the 12 mg dose was to be compared to placebo.

The population to be analyzed in this trial was what the sponsor referred to as the intention-to-treat (ITT) population, defined as those patients who had at least two weeks of seizure frequency data in each of the Baseline and Double-Blind Phases. After the study was completed, the sponsor changed the primary analysis to be what we would typically refer to as a modified ITT (mITT), which includes all patients who had at least one dose of study medication and any effectiveness data.

Results

A total of 388 patients were randomized at 77 centers in Argentina, Canada, Mexico, and the US (N=203, 52%). The following chart displays the disposition of patients randomized:

	Placebo	Peram 8 mg	Peram 12 mg
Randomized	121	133	134
Discontinued	15 (12%)	19 (14%)	34 (25%)
Discontinued due to AE	7 (6%)	9 (7%)	24 (18%)

The baseline seizure frequencies in each group included in the mITT are given in the table below:

	Placebo (N=121)	Peram 8 mg (N=133)	Peram 12 mg (N=133)
Baseline Frequency (per 28 days)			
Mean	26.8	35.5	41.4
Median	13.7	14.3	12

The following table presents the results of the analyses of the primary endpoint for both the protocol specified population (ITT) and the mITT:

Protocol specified ITT

	Placebo (N=119)	Peram 8 mg (N=132)	Peram 12 mg (N=130)
Median % Change From Baseline	-22.9	-32.1	-39.5
Median Difference From Placebo		-11.7	-12.6
P-value		0.08	0.03

m ITT

	Placebo (N=121)	Peram 8 mg (N=133)	Peram 12 mg (N=133)
Median % Change From Baseline	-21	-26.3	-34.5
Median Difference From Placebo		-13.5	-14.2
P-value		0.026	0.016

The following results are presented for the analysis of Responder Rate (for the mITT population, in the Maintenance Phase):

	Placebo (N=121)	Peram 8 mg (N=133)	Peram 12 mg (N=133)
Percent Responders	26.4%	37.6%	36.1%
P-value		0.08	0.09

Study 305

This study utilized the same protocol and design as Study 304. However, in this study, though the initial protocol specified the ITT (sponsor definition as above) as the primary population to be studied, this was changed to the mITT before the data were unblinded.

Results

A total of 386 patients were randomized at 84 centers across Europe, Australia, South Africa, India, the Russian Federation, others, and the US (N=91; 23%). The following chart displays the disposition of these patients:

	Placebo	Peram 8 mg	Peram 12 mg
Randomized	136	129	121
Discontinued	16 (12%)	21 (16%)	28 (23%)
Discontinued due to AE	4 (3%)	11 (9%)	23 (19%)

The following chart displays the baseline seizure frequencies in these patients:

	Placebo (N=136)	Peram 8 mg (N=129)	Peram 12 mg (N=121)
Baseline Frequency (per 28 days)			
Mean	32	37.6	42.3
Median	11.8	13	13.7

The following table presents the results of the analyses of the primary endpoint for both the protocol specified mITT and ITT populations:

m ITT

	Placebo (N=136)	Peram 8 mg (N=129)	Peram 12 mg (N=121)
Median % Change From Baseline	-9.7	-30.5	-17.6
Median Difference From Placebo		-19.1	-13.7
P-value		0.0008	.01

ITT

	Placebo (N=135)	Peram 8 mg (N=126)	Peram 12 mg (N=118)
Median % Change From Baseline	-10.4	-31.3	-17.7
Median Difference From Placebo		-19.5	-13.4
P-value		0.0007	0.01

The following results are presented for the analysis of Responder Rate (for the mITT population, in the Maintenance Phase):

	Placebo (N=136)	Peram 8 mg (N=129)	Peram 12 mg (N=121)
Responder Rate (%)	14.7	33.3	33.9
P-value		0.002	0.0006

As noted earlier, patients were permitted to have been receiving one EIAED. Because these drugs increase the clearance of perampanel by 2-3 fold (with corresponding decreases in plasma levels), an analysis was performed on the subsets of patients defined by whether or not they had been receiving EIAEDs for Studies 304 and 305 combined. About 60% of patients in these two studies combined were receiving an EIAED, and the responses for these two studies combined for the primary outcome is displayed below:

Parameter/ Statistics	Concomitant CBZ, OXC, PHY			Concomitant CBZ or OXC			No Concomitant CBZ, OXC, or PHY		
	Placebo	Perampanel Last Dose		Placebo	Perampanel Last Dose		Placebo	Perampanel Last Dose	
		8 mg	12 mg		8 mg	12 mg		8 mg	12 mg
All partial seizure frequency per 28 days									
Total N	102	94	79	91	77	67	80	64	35
Median frequency – Prerandomization	14.74	10.21	12.78	12.98	10.50	13.66	10.72	13.84	17.18
Median percent change in Maintenance Period	-8.68	-25.82	-22.62	-5.87	-32.37	-27.82	-19.96	-50.63	-54.17
Median difference to placebo (95% CI) ^a		-17.77 (-31.807, -3.872)	-19.21 (-34.269, -4.409)		-25.92 (-40.446, -11.170)	-26.92 (-42.396, -11.338)		-24.37 (-37.818, -10.163)	-33.22 (-47.253, -17.673)
Responder rate									
Total N	102	94	79	91	77	67	80	64	35
Responders, n (%)	21 (20.6)	29 (30.9)	26 (32.9)	17 (18.7)	27 (35.1)	24 (35.8)	12 (15.0)	32 (50.0)	19 (54.3)

Source: 5.3.5.3, Table 14.2.6.6; 5.3.5.3, Table 14.2.6.7.

AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval, N (n) = number of subjects; OXC = oxcarbazepine; PHY = phenytoin.

Note: Subjects who were completers and with actual last dose equal to perampanel 8 or 12 mg were included in the analysis.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Study 306

This study utilized a similar design to that of Studies 304 and 305 (6 week prospective baseline, 6 week titration phase, 13 week maintenance phase). However, in this study, patients were randomized to either placebo or 2, 4, or 8 mg/day of perampanel. Treatment was initiated at 2 mg/day, and in the titration phase, dose was increased by 2 mg/day each week (as in Studies 304 and 305); therefore, patients randomized to 8 mg/day reached their target dose at Week 4, but the baseline phase was still considered 6 weeks.

In this study, as in Study 304, the protocol-specified primary analysis population was the sponsor-defined ITT, and, as in Study 304, this was changed to the mITT after the results were known. However, in contradistinction to Studies 304 and 305, in this study, a more traditional hierarchy of dose comparisons was called for (that is, the first comparison was between 8 mg/day and placebo; if this was significant at an alpha of 0.05, then the 4 mg-placebo contrast was performed, and so on).

Results

A total of 706 patients were randomized across Europe, Asia Pacific, and others. The following chart displays the disposition of these patients:

	Pla	Per 2 mg	Per 4 mg	Per 8 mg
Randomized	185	180	172	169
Discontinued	19 (10%)	26 (14%)	14 (8%)	24 (14%)
Discontinued due to AE	6 (3%)	10 (6%)	5 (3%)	11 (7%)

The baseline seizure frequencies in each group included in the mITT are given in the table below:

	Pla (N=184)	Per 2 mg (N=180)	Per 4 mg (N=172)	Per 8 mg (N=169)
Frequency (per 28 days)				
Mean	23.9	31.2	62.6	32.6
Median	9.3	10.1	10	10.9

The following table presents the results of the analyses of the primary endpoint for both the protocol specified population (ITT) and the mITT:

Protocol specified ITT

	Pla	Per 2 mg	Per 4 mg	Per 8 mg
N	182	177	168	166
Median % Change From Baseline	-10.1	-14.1	-24	-31.3
Median Difference From Placebo		-5.9	-14.8	-20.8
P-value		0.3	0.0008	<0.0001

mITT

	Pla	Per 2 mg	Per 4 mg	Per 8 mg
N	184	180	172	169
Median % Change From Baseline	-10.7	-13.6	-23.3	-30.8
Median Difference From Placebo		-4.4	-13.7	-20.1
P-value		0.4	0.003	<0.0001

The following results are presented for the analysis of Responder Rate (for the mITT population, in the Maintenance Phase):

	Pla	Per 2 mg	Per 4 mg	Per 8 mg
N	184	180	172	169
Percent Responders	17.9	20.6	28.5	34.9
P-value		0.5	0.01	0.000

As with the combined data presented by baseline AEDs (EIAEDs vs non-EIAEDs) for Studies 304 and 305 pooled, the following table presents the analogous results for Study 306:

Statistics	All Partial Seizure Frequency per 28 days				Responder Rate	
	Total N	Median Prerandomization frequency	Median % change in Maintenance Period	Median difference to placebo (95% CI) ^a	Total N	Responder, n (%)
Concomitant CBZ, OXC, PHY						
Placebo	94	11.27	-14.39	--	94	17 (18.1)
Perampanel 2 mg	90	10.71	-16.40	-0.46 (-14.255, 12.712)	90	18 (20.0)
Perampanel 4 mg	84	11.33	-32.66	-11.86 (-24.469, 1.607)	84	22 (26.2)
Perampanel 8 mg	76	8.88	-22.92	-10.82 (-26.083, 4.654)	76	26 (34.2)
Concomitant CBZ or OXC						
Placebo	88	10.59	-13.93	--	88	15 (17.0)
Perampanel 2 mg	80	10.71	-14.44	-0.19 (-14.985, 13.534)	80	15 (18.8)
Perampanel 4 mg	72	11.19	-32.66	-13.46 (-26.396, 0.250)	72	19 (26.4)
Perampanel 8 mg	71	8.88	-24.34	-11.89 (-27.582, 3.806)	71	24 (33.8)
No concomitant CBZ, OXC, PHY						
Placebo	72	8.23	-16.04	--	72	14 (19.4)
Perampanel 2 mg	70	8.88	-22.81	-8.15 (-24.315, 7.057)	70	18 (25.7)
Perampanel 4 mg	69	9.56	-21.90	-15.31 (-31.125, 1.334)	69	24 (34.8)
Perampanel 8 mg	53	11.61	-40.27	-27.60 (-44.872, -11.385)	53	21 (39.6)

Source: 5.3.5.3, Table 14.2.6.9; 5.3.5.3, Table 14.2.6.10; 5.3.5.3, Table 14.2.6.11; 5.3.5.3, Table 14.2.6.12.

AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval, N (n) = number of subjects; OXC = oxcarbazepine; PHY = phenytoin.

Note: Subjects who were completers and with actual last dose equal to perampanel 8 or 12 mg were included in the analysis.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

It is clear that there is a dose related increase in discontinuations due to adverse events.

More specifically, the following charts display relevant information on discontinuation and/or down-titration in the combined dose groups from the three controlled trials in patients with epilepsy:

Percent of Patients Discontinuing due to AEs

	Placebo	2 mg	4 mg	8 mg	12 mg
Study 304	6.6%			6.8%	19.4%
Study 305	4.4%			9.3%	19%
Study 306	3.8%	6.7%	2.9%	7.1%	

Percent of Patients Reaching Their Assigned Dose and Either Discontinued or Down-Titrated in the Combined Studies 304, 305, and 306

Placebo	2 mg	4 mg	8 mg	12 mg
11.3%	14.5%	10.1%	25.1%	24.3%

Percent of Patients Who Achieved Their Assigned Dose

Placebo	2 mg	4 mg	8 mg	12 mg
100%	99%	98%	96%	72.5%

Percent of Patients Whose Last Dose Was Their Target Dose

2 mg	4 mg	8 mg	12 mg
98%	93.6%	81%	61.2%

Modal Dose by Assigned Dose

	Assigned Dose			
Modal Dose	2 mg	4 mg	8 mg	12 mg
< 4 mg	+16.7%			
4 mg		+10.5%		
>4-8 mg			+4.4%	
>8-12				-26.2%

Percent of Patients Reaching Their Target Dose by concomitant AEDs:

Baseline AEDs	2 mg	4 mg	8 mg	12 mg
EIAEDs	83%	90%	75%	62%
No EIAEDs	88%	86%	67%	42%

Safety

The sponsor submitted data from 52 clinical studies (completed and on-going) according to the following categories:

Study Type	Number of Studies (N)
Phase 1	27 (916)
Epilepsy	10 (1651)
Non-Epilepsy	15 (2717)

A total of 5284 patients received at least one dose of perampanel. A total of 2482 patients received treatment for at least 6 months (N=1231 epilepsy), 1552 received treatment for at least one year (N=996 epilepsy), and 519 patients received treatment for at least 2 years (N=453 epilepsy).

Among epilepsy patients (N=1651), the following chart, taken from Dr. Doi's Table 12, displays the Mean and Median Durations of Exposure by Modal Dose.

Duration of Exposure (weeks)	Modal Dose			
	<4mg	4mg	>4-8mg	>8-12mg
N	153	192	354	952
Mean	28	51	57	89
Median	11	24	37	92

A total of 78% of patients in the highest Modal Dose group were treated for at least one year.

The corresponding table for non-epilepsy patients (N=2717) is presented below:

Duration of Exposure (weeks)	Modal Dose			
	<4mg	4mg	>4-8mg	>8-12mg
N	1048	1441	188	40
Mean	26	26	29	49
Median	14	30	16	49

As can be seen, most of the non-epilepsy patients were treated with the lower doses (4 mg or less) and for shorter durations than the patients with epilepsy.

Deaths

There were a total of 30 deaths in perampanel-treated patients in the development program; 8 in patients in epilepsy studies, 22 in patients in non-epilepsy studies (18 in PD studies, 4 in neuropathic pain studies).

The mortality was 3.5 deaths/1000 patient-years in epilepsy and 13.2 deaths/1000 patient-years in the non-epilepsy population.

In epilepsy, none of the deaths occurred in the controlled trials (one died in the pre-randomization phase of Study 304 and did not receive drug). A total of 11 deaths in perampanel-treated patients occurred in double blind trials (non-epilepsy). The relative risk for death compared to placebo in all double blind trials was 0.61 (that is, the mortality was greater in controlled trials on placebo than drug).

In patients treated for epilepsy, all were taking 12 mg/day at the time of their death. There were 3 sudden deaths: 1 was classified as Sudden Unexplained Death in Epilepsy (SUDEP), one was considered cardiac arrest, and one was related to an unknown cause. The other 5 were related to disparate causes, and had no obvious relationship to treatment (car accident, cerebral hemorrhage, pneumonia, traumatic hydrocephalus, neonatal death), and treatment durations ranged from 55 days (car accident) to 616 days, with all other deaths occurring after at least about 6 months of treatment. The three sudden deaths are briefly described below:

- 1) a 48 year old woman with morbid obesity, hypertension, hypercholesterolemia, hypothyroidism, ascites, and edema was treated for 705 days when she was found dead. Myocardial infarction was listed as the cause of death, though no autopsy was performed.
- 2) a 54 year old man with no significant medical history was found dead in bed by his wife on day 55 of treatment. The cause of death was listed as SUDEP.
- 3) A 27 year old woman who died suddenly on day 172 of treatment. The cause of death was listed as unknown.

The non-epilepsy patients who died were older (mean age 69 compared to 44 in the patients with epilepsy who died) and had more risk factors than the epilepsy patients. The causes of death in PD controlled trials in perampanel-treated patients (N=9) did not differ substantially from those of the placebo patients (e.g., myocardial infarction, pneumonia). In PD open-label studies, there were similar causes of death, with treatment durations ranging from 35 days to 892 days. Only three patients who died were treated for less than 258 days:

- 1) a 77 year old man with a history of MI who was treated for 35 days. He was found dead 35 days after treatment with perampanel was discontinued
- 2) a 79 year old man with a recent history of MI, confusion, renal impairment, hypotension experienced acute left ventricular failure on treatment day 20, and cardiac failure on day 60. Drug was discontinued on day 63, and he died 11 days later.
- 3) an 83 year old woman with a history of coronary artery disease who was found unresponsive 22 days after her last dose of drug (which was on day 83).

Serious Adverse Events (SAEs)

The following charts display the rates of SAEs in both the epilepsy Phase 3 controlled trials and in the non-epilepsy controlled trials:

Epilepsy Phase 3 controlled trials

	Placebo	2 mg	4 mg	8 mg	12 mg
Epilepsy	5%	3.3%	3.5%	5.6%	8.2%

The following chart displays the incidence of categories of SAEs by dose in the epilepsy controlled trials that could possibly be considered dose related:

Event Category	Pla	<4mg	4mg	>4-8mg	>8-12mg
N	510	192	273	431	293
Psychiatric	0.8%	1.6%	0.4%	0.5%	2.4%
Injury/Poisoning	0.6%	0.5%	0	1.2%	2.4%
Musculoskeletal	0	0	0	0.9%	0
Renal and Urinary	0	0.5%	0	0	0.7%
GI Disorder	0.2%	0	0	0.2%	0.7%
Reproductive/Breast	0	0	0	0	0.7%

The following chart displays the incidence of SAEs in epilepsy Phase 3 controlled trials that occurred in 2 or more patients and were more frequent than in the placebo group:

Event	Placebo	Perampanel
N	510	1189
Any SAE	22 (4.3%)	57 (4.8%)
Dizziness	0	3
Somnolence	0	3
Aggression	0	3
Head Injury	0	3
Facial bone fracture	0	2
Cholelithiasis	0	2
Wound infection	0	2

Non-epilepsy controlled trials

	Placebo	<4mg	4mg	>4-8mg
Parkinson's Disease	7%	6.4%	7.2%	14.5%
Neuropathic Pain	3%	2.8%	2.9%	10.6%

The following chart displays the categories of SAEs that occurred more frequently than 1% in all studies:

Category	Epilepsy	Non-epilepsy
N	1651	2717
Nervous system	6.7%	3%
Injury, Poisoning	3.9%	1.9%
Psychiatric Disorders	3.6%	1.6%
Infections	2.1%	1.7%
GI disorders	1%	1.1%
Cardiac Disorders	0.7%	1.7%
Musculoskeletal	0.6%	1.1%

Discontinuations

The following charts display various incidences of reasons for discontinuations in epilepsy and non-epilepsy studies. The following charts display various aspects of discontinuations from clinical trials.

Adverse Events Leading to Discontinuations in Epilepsy Controlled Trials

Event	Placebo	Peram
N	510	1189
Any AE	1.6%	2.5%
Dizziness	0.8%	2%
Somnolence	0.2%	0.8%
Vertigo	0	0.7%
Fatigue	0	0.7%
Ataxia	0	0.6%
Rash	0	0.6%
Aggression	0	0.4%
Anger	0	0.3%

The following table displays the incidence of total discontinuations and discontinuations due to adverse events by dose in the controlled epilepsy trials:

	Placebo	<4mg	4 mg	>4-8mg	>8-12mg
N	510	192	273	431	293
Any D/C	11.4%	13.5%	8.4%	14.8%	22.5%
Due to AE	4.3%	5.2%	3.7%	7.2%	16.7%

In the non-epilepsy studies 28% of perampanel and 23% of placebo-patients discontinued treatment. A total of 15.3% of perampanel and 9.7% of placebo-treated patients discontinued due to adverse events.

The following table displays the incidence of all discontinuations and discontinuations due to AEs by modal dose:

	Placebo	<4mg	4mg	>4-8mg
N	1078	908	814	291
Any D/C	22.8%	20.6%	30.2%	44.7%
Due to AE	9.7%	10.5%	14.9%	31.6%

The following chart displays the categories of AEs that led to discontinuation by modal dose in the epilepsy controlled trials:

	Pla 510	<4mg 192	4mg 273	>4-8mg 431	>8-12mg 293
Category					
Nervous System	3.1%	2.1%	1.5%	4.2%	10.6%
Psychiatric	1.4%	2.6%	0.4%	0.9%	5.8%
General	0.4%	1.6%	1.1%	0.9%	3.4%
Gastrointestinal	0.4%	0.5%	0.4%	0.9%	1.4%
Ear and Labyrinth	0	0	0	0.2%	1.0%
Eye Disorders	0	0	0	0.2%	1.0%
Skin	0	0	1.1%	0.9%	1.0%

Significant events

Dr. Doi has identified several types of adverse events that were prominent and of clinical significance. The adverse events that were serious and/or responsible for drug discontinuation will largely be discussed in these sections.

Psychiatric Adverse Events

The following chart displays the incidence in the epilepsy controlled trials of psychiatric adverse events, those that were considered serious, and those that led to discontinuation.

Psychiatric Adverse Events

	Placebo	Perampanel
All AEs	12.4%	15.3%
SAEs	0.9%	1.2%
Discontinuations	1.6%	2.5%

In all epilepsy treated patients, the analogous chart is:

	Perampanel
All AEs	28.8%
SAEs	3.6%
Discontinuations	6%

The following chart displays the incidence of the primary specific psychiatric adverse events by modal dose in the epilepsy controlled trials:

Event	Plac	<4mg	4mg	>4-8mg	>8-12mg
Irritability	2.9%	3.9%	4.1%	6.7%	11.8%
Anxiety	1.1%	2.2%	1.7%	3.0%	3.5%
Aggression	0.5%	0.6%	0.6%	1.6%	3.1%
Skin Lacer- Ation	1.6%	0.6%	0	1.6%	2.4%
Anger	0.2%	0	0	1.2%	2.8%
Affect Labile	0	0	0	0	0.8%
Sleep Disor	0.2%	1.1%	0.6%	1.4%	0.8%
Abnl Behav	0	0	0	0.5%	0.8%
Panic Attack	0.2%	0.6%	0	0.2%	0.8%

Dr. Doi has performed additional analyses of terms related to Hostility/Aggression, and has generated the following tables:

	Placebo	Perampanel
TEAEs	5.7%	11.8%
SAEs	0.2%	0.7%
Discontinuations	0.7%	1.6%
Dose Reduction	0	1.8%
Severe	0	1.3%

She has reviewed numerous narratives of patients who experienced these events, and has determined that patients in the perampanel group had a lower rate of prior psychiatric history than placebo patients, and also an essentially comparable rate of using concomitant Keppra (an AED also known to be associated with similar events). Some of these events were associated with physical assault, property damage, and at least one case of a threat with a weapon, though in any given case it is difficult to attribute the specific behavior to drug. Briefly, the following cases of concern are given as examples (Dr. Doi provides narrative of cases of concern in her review, pages 95-101, Table 49):

- 1) a 57 year old man with a history of “situational anxiety” who received 8 mg/day and on Day 45 of treatment experienced homicidal ideation, anger, and rage. He reported looking for his shotgun. He was reported to have been unable to think clearly, and was described as “bouncing off the walls”. Perampanel was discontinued, and the reaction resolved within 24 hours.

- 2) A 42 year old woman with a history of anxiety and depression was hospitalized for homicidal and suicidal ideation on Day 259 of open-label treatment on 12 mg/day. The dose was reduced and the events resolved in 5 days.
- 3) A 57 year old man with a history of cerebral palsy, a CVA experienced belligerence on Day 33 on the 12 mg dose, who again on Day 40 hit the office staff and bit his sister's finger. The events resolved 5 days after perampanel was discontinued (though he was also treated with olanzapine).
- 4) A 56 year old woman with mental retardation was hospitalized on open-label day 79 (12 mg; she was on the 8 mg dose during the double-blind trial) for attacking her caregiver and being physically aggressive towards her mother. She had discontinued perampanel 4 days prior to these events, and the events resolved 8 days after they occurred, though she was also treated with antidepressants and antipsychotics.
- 5) A 12 year old boy with a history of aggression had multiple episodes of aggression starting on open-label day 122 (after having received 8 mg/day in the double-blind trial) beat his mother and threatened to kill his family on Day 483 (his fifth episode of aggression). This episode resolved about a month later, and perampanel was continued (last reported dose on Day 697).

In the overwhelming majority of cases, the drug was continued, with no recurrence of the event in the Phase 3 Epilepsy controlled trials. In a few cases, however, the same event, or one similar, recurred. Recurrences only occurred in the 8 and 12 mg/day groups. Most of the events in the 8 and 12 mg/day groups occurred during titration, as did most of the discontinuations.

Although there were no differences in the incidence of suicidal ideation or attempts between the placebo and perampanel patients in the Epilepsy Phase 3 controlled trials, there were a total of 23 such events in the entire database of perampanel treated patients. A total of 17 of these events were considered serious, and a total of 12 patients discontinued due to these events. There were no suicides.

The following chart displays the psychiatric adverse events considered SAEs:

Event	Placebo (N=442)	Perampanel (N=1038)
Aggression	0	0.3%
Adjustment Disorder	0	0.1%
Belligerence	0	0.1%
Confusional State	0	0.1%
Disorientation	0	0.1%
Impulse-control disorder	0	0.1%
Suicidal ideation	0	0.1%

Psychiatric adverse events that led to discontinuation:

Event	Placebo	Perampanel
Aggression	0	0.5%
Anger	0	0.4%
Anxiety	0	0.3%
Confusional State	0	0.2%
Suicidal Ideation	0	0.2%

Nervous System Adverse Events

The most common adverse events in clinical trials involved the nervous system.

The following chart displays the incidence of AEs, SAEs, and discontinuations due to AEs involving the nervous system:

	Placebo N=442	Perampanel N=1038	All Epilepsy
Any AE	31%	51%	71%
SAEs	2.5%	1.8%	6.7%
Discontinuations	2.9%	5.1%	10.7%

SAEs in the Epilepsy controlled trials

Event	Placebo N=510	Perampanel N=1189
Dizziness	0	0.3%
Somnolence	0	0.3%

Discontinuations Due to Nervous System AEs

Event	Placebo N=442	Perampanel N=1038
Dizziness	0.9%	2.1%
Somnolence	0.2%	1%
Ataxia	0	0.7%
Dysarthria	0	0.4%
Balance Disorder	0	0.3%
Coordination Abnl	0	0.2%

The following table displays the specific Nervous System Adverse Events reported in the Epilepsy Phase 3 controlled trials by assigned dose:

Event	Pla	2 mg	4mg	8 mg	12 mg
N	442	180	172	431	255
Dizziness	9	10	16	32	43
Somnolence	7	12	9	16	18
Fatigue	5	4	8	8	12
Ataxia	0	0	1	3	8
Vertigo	1	3	4	3	5
Dysarthria	0	0	1	3	4
Gait Disturbance	1	1	1	4	4
Balance Disorder	0.5	0	0	5	3
Hypoesthesia	1	1	0	0	3
Parasthesia	1	1	0	0.5	2
Asthenia	0.5	1	1	2	2
Memory Impairment	1	1	0	1	2
Coordination Abnl	0	0	1	0.5	2
Confusional state	0.5	1	1	1	2
Lethargy	0.5	0	0	1	1
Disorientation	0.5	0	0	0.5	1

Few of these events were considered SAEs or led to discontinuation:

Event	Placebo	Perampanel
N	442	1038
Dizziness group		
SAE	0	0.3%
Discontinuations	1%	3.5%
Somnolence group		
SAE	0	0.3%
Discontinuations	0.5%	2%
Cognitive group		
SAE	0.2%	0.3%
Discontinuations	0	0.7%
Paresthesia group		
SAE	0	0
Discontinuations	0	0.1%

Most of the adverse events occurred in the titration phase,

Falls

The following table displays the incidence of falls in the Epilepsy Phase 3 controlled trials by dose:

	Placebo	<4mg	4mg	>4-8mg	>8-12mg
Epilepsy	3.4%	1%	2%	5%	10%
Non-epi	3%	5%	5%	11%	

The greater incidence of falls at any given dose in the non-epilepsy population likely reflects, among other factors, the older population in the non-epilepsy studies, an observation borne out when the studies were analyzed by age:

	Placebo	Perampanel
Epilepsy		
Elderly	0/8	5/20 (25%)
Adults	14/396 (3.5%)	46/946 (5%)
Adolescents	1/38 (2.6%)	2/72 (2.8)
Non-epilepsy		
Elderly	15/450 (3.3%)	54/905 (6.0)
Adults	22/629 (3.5%)	56/1108 (5.1%)

Dr. Doi has observed that the increase in falls on drug compared to placebo was not related to falls that occurred related to seizure events.

The following chart displays the incidence of SAEs related to injuries in the Epilepsy controlled trials:

Event	Placebo	Perampanel
N	510	1189
Any Injury	0.6%	1.1%
Head injury	0	0.3
Facial Bone fracture	0	0.2%

Weight gain

The following chart displays the mean change in weight in kgs (for adults) by dose in the Epilepsy Phase 3 controlled trials:

Placebo	<4 mg	4mg	>4-8mg	>8-12mg
N=401	N=166	N=162	N=398	N=235
0.31	0.38	0.96	1.23	1.57

The following chart displays the percent of adults who gained various percentages of their baseline body weight in the Epilepsy Phase 3 controlled trials:

Category	Placebo	Perampanel
N	401	961
Mean Change	0.3 kg	1.12 kg
>7%	4.5%	9.1%
>15%	0.2%	0.9%
>25%	0	0.1%

A total of 4% of perampanel- and 1% of placebo-treated patients reported weight gain in the Epilepsy Phase 3 trials, though there were similar rates (1%) of increased appetite in both groups.

Skin

The following chart displays the rate of SAEs and Discontinuations related to rash in the Epilepsy controlled trials:

	Placebo	Perampanel
N	510	1189
SAE	0	0.1%
Discontinuations	0	0.7%

Common Adverse Events

The following table presents the major adverse events seen in the Epilepsy Phase 3 controlled trials, by assigned dose:

Event	Pla	2mg	4mg	8mg	12mg
N	442	180	172	431	255
Dizziness	9	10	16	32	43
Somnolence	7	12	9	16	18
Headache	11	9	11	11	13
Fatigue	5	4	8	8	12
Irritability	3	4	4	7	12
Fall	3	1	2	5	10
Ataxia	0	0	1	3	8
Nausea	5	2	3	6	8
Vertigo	1	3	4	3	5
Gait Disturbance	1	1	1	4	4
Vomiting	3	3	2	3	4
Weight Increased	1	2	4	4	4
Decreased appetite	2	1	1	2	4
Anxiety	1	2	2	3	4
Vision Blurred	1	0	1	3	4
Dysarthria	0	0	1	3	4
Diplopia	1	1	1	1	3
Head Injury	1	1	1	1	3
Hypersomnia	0	1	1	2	3
Hypoesthesia	1	1	0	0	3
Anger	0	0	0	1	3
Aggression	1	1	1	2	3
Balance Disorder	1	0	0	5	3
Increased appetite	1	1	0	1	3

Adverse Event Rates by background AEDs

Because of the 2-3 fold increase in plasma levels of perampanel when taken together with EIAEDs, Drs. Doi and Xing have examined the incidence of all TEAEs, SAEs, discontinuations, and, specifically, hostility-related AEs by background AEDs. The following table displays the pooled results for Studies 304 and 305:

Category	Pla	8 mg	12 mg
Total N	257	262	255
Patients with:			
With inducers	65%	68%	67%
Without inducers	35%	32%	33%
TEAEs			
With inducers	74%	85%	88%
Without inducers	78%	92%	92%
SAEs			
With inducers	5%	7%	6%
Without inducers	6%	7%	12%
Discontinuations			
With Inducers	6%	7%	13%
Without inducers	4%	11%	32%
Hostility TEAEs			
With inducers	11%	15%	19%
Without inducers	14%	25%	32%

Laboratory Tests

There were few systematically abnormal laboratory tests.

The following chart displays the percent of patients with normal hematology values at baseline that shifted to low values on treatment in the Epilepsy Phase 3 controlled trials:

Parameter	Placebo	Perampanel
N	442	1018
Hemoglobin low	3.5%	5%
Neutrophils low	4.4%	6.5%

The following table displays the rate of hematologic adverse events in the Epilepsy controlled trials:

Event	Placebo	Perampanel
N	510	1189
Anemia	0.2%	0.8%
Neutropenia	0	0.6%
Leukopenia	0	0.5%

The following chart displays the incidence of potentially significant changes in various analytes in the Epilepsy Phase 3 controlled trials:

Laboratory test	Placebo	Perampanel
AST >3 X ULN	0	0.3%
Bilirubin > 1.5 X ULN	0	0.2%
Glucose <3 mmol/L	0.5%	1.7%

The following chart displays the shifts from normal baseline to abnormal values in both the Epilepsy Phase 3 and Phase controlled trials:

Laboratory Tests	Phase 3		Phase 2	
	Pla	Peram	Pla	Peram
Calcium low			1.5%	4.6%
CPK High	4.2%	6.9%	1.6%	14.4%
Phosphate low	0.7%	1.7%		
Potassium high			1.5%	4%
Cholesterol high	2.9%	8.3%		
Cholesterol borderline	8.8%	23.6%		

Vital signs

There were no consistent, significant, systematic changes in blood pressure or pulse.

EKG

A thorough QT study was performed evaluating the effects of perampanel 12 mg/day (and moxifloxacin as a positive control). The study was shown to have assay sensitivity, and the changes in QT interval did not reach the regulatory threshold (that is, the upper bound of the difference between the 12 mg dose and placebo did not exceed 10 ms).

Clinical Pharmacology

Oral absorption of perampanel is essentially complete, with a median T_{max} of 0.5-2.5 hours. It is bound 95-96% primarily to albumin and alpha1-acid glycoprotein (and to a much lesser extent to gamma-globulin). It is extensively metabolized by oxidative metabolism; some metabolites are glucuronidated. Although in vitro studies suggest that CYP3A4/5 is a major metabolizing enzyme, an in vivo study with ketoconazole resulted in minor increases (about 20%) in perampanel levels. Because oral clearance of perampanel was increased three-fold by concomitant carbamazepine (an AED known to induce multiple enzymes), other metabolizing enzymes must play a role in perampanel metabolism. Less than 0.2% of parent drug was recovered in urine up to 48 hours after dosing.

The terminal half-life of perampanel is about 100 hours.

Women have about a 30% increase in AUC compared to men, and the elderly had similar CL/F to younger adults (adolescents have a slightly higher CL/F than adults).

Total AUC of perampanel was about 50% higher in patients with mild hepatic impairment compared to healthy controls, and was about 2.5 times higher in patients with moderate hepatic impairment compared to healthy controls. The half-life was about 300 hours in both of these subsets of patients.

CL/F was decreased slightly in patients with mild renal impairment compared to healthy controls (about 27%).

In vitro, perampanel did not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, UGT1A1, UGT1A4, or UGT1A6. It did not induce CYP1A2, and is a weak inducer of 2B6, and 3A4. At high concentrations, it was an inducer of 2B6, but was not tested at therapeutic levels for its effect on CYP2B6.

It is not a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT2,)AT3, OAT4, OCT1, OCT2, or OCT3. It is a weak inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1, and OCT3. It induces OAT2, but no clinically important drug interactions with substrates of these transporters are expected.

Pharmacology

There are no outstanding pharmacology deficiencies that would preclude approval. Dr. Toscano has recommended that the sponsor be required to perform an in vitro study in Phase 4 to determine if perampanel binds to human aorta, based on its known ability to bind to elastin. Dr. Freed, however, argues that such a study is unnecessary, given the unknown implications of such binding (were it to occur) to any clinical untoward consequences. I agree that the study need not be required.

Perampanel produced visceral abnormalities in the offspring of pregnant rats, as well as embryoletality and decreased fetal weight. When perampanel was given to pregnant rabbits, it produced embryoletality. For these reasons, Dr. Freed recommends that it be labeled as Pregnancy Category C.

CMC

There are no outstanding CMC deficiencies that preclude approval.

CSS

 (b) (4)
Final scheduling will not be completed prior to the PDUFA due date of 10/22/12. If the application is approved before a final decision about scheduling is made, the sponsor may not legally market the drug.

Comments

The sponsor has submitted the results of three randomized controlled trials that they conclude provide substantial evidence of effectiveness for perampanel as adjunctive therapy in patients 12 years old and older. In addition, they have submitted safety data that they conclude establish the safety of perampanel at doses up to and including 12 mg/day in this population.

Regarding effectiveness, in Study 304 the sponsor proposed that the lower of the two doses studied, 8 mg/day, was to be tested first (presumably because they predicted that the number of discontinuations at the 12 mg dose might have

rendered that comparison non-significant), and only if the 8 mg-placebo contrast reached statistical significance, was the 12 mg-placebo contrast to be made. Further, the primary analysis was to include only those patients who had two weeks of data during the Maintenance Phase. Under these conditions, the 8 mg-placebo contrast did not achieve statistical significance, and therefore the 12 mg-placebo contrast (which did achieve nominal significance) should not have been made.

Both of these maneuvers are non-traditional, however. In particular, the primary study population described in the protocol is one that we would ordinarily not accept: In order to preserve randomization, we would typically require that the sponsor include in its primary analysis all patients who had at least one dose of study drug and efficacy data collected. When this was done, both doses reached statistical significance. In my view, it is appropriate to analyze all of these trials in this more appropriate way. When this is done, doses from 4-8 mg/day are seen to be effective.

Importantly, as has been noted, EIAEDs reduce the plasma levels of perampanel 2-3 fold, and the trials did not alter the dosing in study patients according to their baseline AEDs. About 60% of patients were taking an EIAED at baseline, and this had a profound effect on treatment response. It is clear that patients receiving EIAEDs had a much lower treatment response than those not taking an EIAED at baseline (for example, in Studies 304 and 305 combined, the median percent difference from placebo at 12 mg was about -19% in patients taking EIAEDs, compared to -33% in non-EIAED patients). There is a clear increase in response between 4 and 8 mg/day (in both EIAED and non-EIAED patients), and there is a considerably smaller, though still somewhat evident, dose response between 8 and 12 mg/day (in both EIAED and non-EIAED patients). Nonetheless, the treatment effect is much smaller in patients taking EIAEDs than in non-EIAED patients for any given daily dose. Although it is evident that the effect on seizure frequency is similar for a given plasma level (regardless if the patient is on an EIAED or not), it is clear that, for any given dose, patients taking an EIAED achieve a given plasma level of drug far less frequently than do patients not taking an EIAED, and therefore that the sponsor has not adequately explored the maximum effective dose range in patients taking EIAEDs. It does appear, however, that they have identified, if not the maximum tolerated dose, at least a dose relatively close to the maximum tolerated dose, in patients not taking EIAEDs. For example, the percent of patients who were randomized to the 12 mg dose who even reached that dose was about 42% in patients not taking EIAEDs (compared to about 62% in the EIAED patients).

Regarding safety, perampanel causes typical adverse reactions referable to the nervous system (e.g., dizziness, ataxia, diplopia), as well as somnolence, and an increased incidence of falls, but few other significant adverse events, with one major exception (see immediately below). As with effectiveness, though, it should be noted that the incidence of adverse reactions is also dependent upon

whether patients were taking EIAEDs or not.

Perampanel clearly causes, in a small number of patients, significant psychiatric/behavioral symptoms. These symptoms include, most importantly, anger, aggression, and hostility, and resulted in some cases in homicidal ideation and physical assaults.

As noted earlier, other AEDs also cause similar reactions (for example, Keppra). However, at least some of the reactions seen with perampanel seem more severe and serious than with other drugs. For example, the labeling for Keppra does not include homicidal ideation, whereas with perampanel, there are at least three cases that were coded as such, and at least a few more cases that appear to be similar (though they were not coded by the sponsor as such). Although I believe that it is impossible, in any specific case, to conclude with certainty that perampanel was the cause, it is also clear that perampanel does cause aggression and hostility in some patients, and homicidal ideation can be considered to fall in that continuum of behaviors, so that it is certainly plausible (if not proven) that these events could have been caused by perampanel.

Based on these considerations, we recommend that the application be approved, with a recommended dose range of 8-12 mg/day (although 4 mg has been shown to be effective, and should be described in labeling, the effect at that dose is far below that seen at 8 mg/day). However, we recommend that the product labeling include detailed descriptions of the effectiveness data according to whether or not the patient is receiving an EIAED. At this time, we cannot recommend daily doses greater than 12 mg/day in any patient, given that higher doses have not been evaluated in any controlled epilepsy trial. However, we also recommend that the sponsor study such doses in a well controlled trial (see below).

We also recommend that the product labeling include a Boxed Warning describing the psychiatric and behavioral adverse events that perampanel can cause, including homicidal ideation. As noted above, although other AEDs can cause similar reactions, those seen with perampanel seem (at least in some patients) more severe and serious than those seen with other AEDs. A Boxed Warning will alert prescribers to the potential for perampanel to cause these events, and that they are more severe than those seen with other AEDs.

[REDACTED] (b) (4)

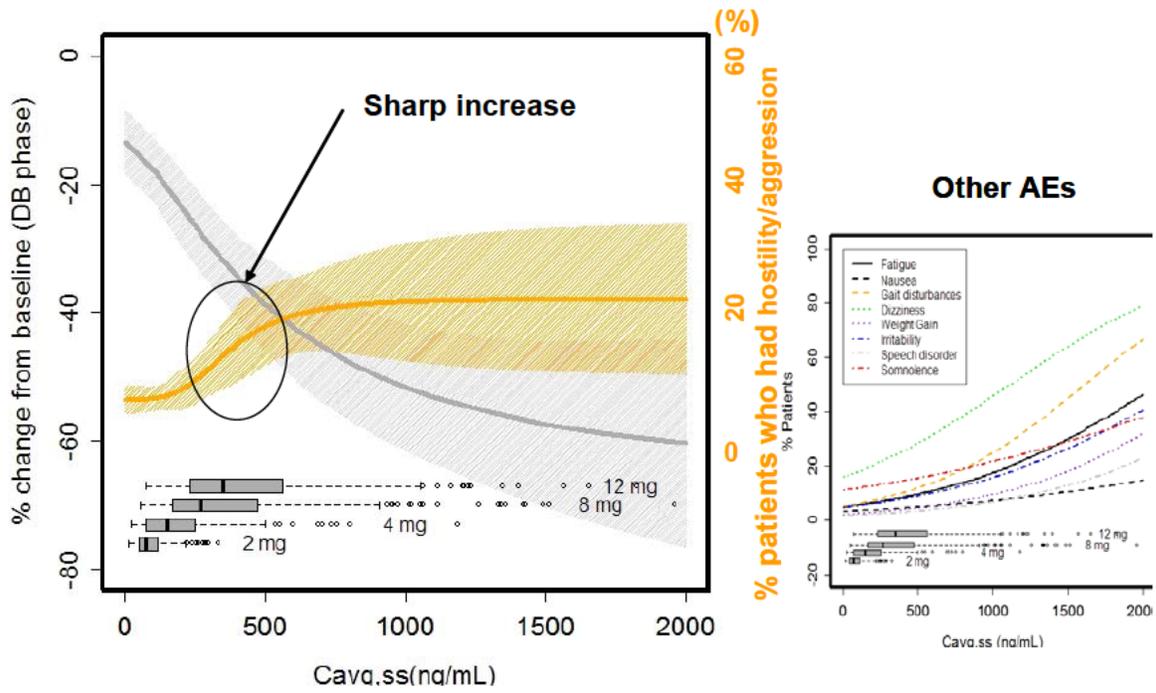
This issue is still under review, and, though we recommend that the application be approved, we recognize that the drug cannot be marketed until a final decision on scheduling has been made.

Finally, we will require, as Post Marketing Requirements (PMRs), that the following studies be performed after approval:

- 1) A pharmacokinetic study in pediatric patients ages 1 month to <2 years old
- 2) A pharmacokinetic study in pediatric patients ages 2 to <12 years old
- 3) A randomized controlled trial in pediatric patients ages ^(b)₍₄₎ to <12 years old with long term safety extension
- 4) A randomized controlled trial in pediatric patients 1 month to <4 years old with long-term safety extension
- 5) An in vitro study to evaluate if CYP1A2, 2B6, 2C8, 2C19, 2C9, and/or 2D6 contribute to the metabolism of perampanel
- 6) An in vitro study to determine if non-CYP enzymes contribute to the metabolism of perampanel
- 7) An in vitro study to evaluate the effects of perampanel on CYP2B6
- 8) A randomized controlled trial to evaluate the effective (and safe) dose range of perampanel as adjunctive therapy in patients with partial seizures taking EIAEDs
- 9) A prospective physical dependence trial in patients with epilepsy

We have discussed product labeling and these PMRs with the sponsor; they have agreed to labeling and these PMRs. For these reasons, we recommend that the application be approved.

Russell Katz, M.D.



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/s/

RUSSELL G KATZ
10/22/2012