CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

SUMMARY REVIEW

Deputy Office Director Decisional Memo

Date	October 28, 2008
From	Ellis F. Unger, M.D., Deputy Director (acting), ODE1
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	22-253, 22-254, [redacted] b(4) 000
Applicant Name	Schwarz Biosciences
Date of Submission	September 28, 2007
PDUFA Goal Date	October 28, 2008 (extended from July 28, 2008)
Proprietary Name / **Established (USAN) Name**	Vimpat Lacosamide
Dosage Forms / Strength	Tablets 50-, 100-, 150-, and 200-mg; 200 mg/20mL single-use vial for intravenous use
Proposed Indication(s)	1. For the treatment of epilepsy as adjunctive therapy in subjects with partial onset seizures aged 16 years and older (tablets) b(4) 2. ….when oral administration is temporarily not feasible (200 mg/mL IV)
Action:	Approval for 22-253, 22-254· [redacted] b(4)

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Norman Hershkowitz
Statistical Review	Tristan Massie
Safety Review	Lourdes Villalba, Sally U. Yasuda (supervisory)
Pharmacology Toxicology Review	BeLinda A. Hayes, Ed Fisher, Lois M. Freed (supervisory), Paul C. Brown (tertiary)
CMC Review/OBP Review	Wendy I. Wilson, Prufull Shiroman, Blair Fraser (supervisory)
Microbiology Review	Vinayak B. Pawar
Clinical Pharmacology Review	Veneeta Tandon, Lei Zhang, Emmanuel Fadiran, and Hao Zhu
DMEPA	Loretta Holmes
DSI	Sheryl Gunther
CDTL Review	Norman Hershkowitz
OSE/DRISK	Sharon R. Mills
OSE/ Division of Medication Errors	Judy Park
Cardiac safety	Stephen M. Grant

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE=Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

I concur with Dr. Russell Katz, Director, Division of Neurology Products, in his recommendation to approve Vimpat (lacosamide) tablets for adjunctive treatment of partial seizures in adult patients with epilepsy, and to approve Lacosamide Injection for the same indication when oral administration is temporarily not feasible.

There were no notable disagreements or issues between disciplines (microbiology, CMC, nonclinical pharmacology/toxicology, clinical pharmacology, clinical, biostatistical) or within review discipline hierarchies (primary, secondary, tertiary reviewers).

The evidence of effectiveness and safety was based on studies of the oral tablet form (NDA 22-253). The NDAs for the [redacted] intravenous injection were supported by bioequivalence to the tablet. [redacted] b(4)

Initial review of the NDA raised concern regarding a multiorgan hypersensitivity syndrome, and the Division asked the sponsor to submit more detailed analyses of this issue. They submitted their analysis on 7/16/08, resulting in a 3-month extension of the PDUFA goal date. The sponsor also submitted NDA [redacted] for the use of lacosamide for the treatment of the pain of diabetic peripheral neuropathy. That application was reviewed by the Division of Analgesic, Anesthetic, and Rheumatology Products (DAARP), and not approved, [redacted] b(4)

Effectiveness: The applicant established lacosamide's effectiveness as adjunctive therapy in partial-onset seizures (with or without secondary generalization) in three 12-week, randomized, double-blind, placebo-controlled, multicenter trials in adult patients (studies 667, 754, and 755). The studies were similar in their designs and analytic plans.

Study 667 compared doses of 200-, 400-, and 600-mg/day with placebo. Study 754 compared doses of 400- and 600-mg/day with placebo. Study 755 compared doses of 200- and 400-mg/day with placebo. All three studies included an 8-week baseline period to establish seizure frequency prior to randomization, and ensure a frequency of at least 4/week with no seizure-free period exceeding 21 days, despite use of 1 to 3 concomitant antiepileptic drugs. The baseline period was followed by a 6-week titration phase (only 4 weeks long in study 755). Subjects randomized to lacosamide were begun at a dose of 100 mg/day (50 mg given twice daily), and increased weekly in 100 mg/day increments to the target dose. All 3 trials included a 12-week maintenance phase, during which patients were to remain on a stable dose of lacosamide.

The primary outcome measure was reduction from baseline in 4 week seizure frequency during the maintenance phase, analyzed by an ANCOVA with terms for treatment and region, based on log-transformed seizure frequency, with log-transformed average baseline seizure frequency as the covariate. Testing was to be hierarchical, with the highest dose tested first, followed by progressively lower doses. The sponsor's results are shown in Table 1.

Table 1: Basic Features and Efficacy Endpoints – Studies 667, 754, 755

Study	Location	Daily dose	N	% reduction vs. placebo	p-value	95% CI
667	US, Europe	200 mg	107	14.6%	0.101	(-3.2, 29.4)
		400 mg	107	28.4%	0.0023	(11.3, 42.2)
		600 mg	105	21.3%	0.0084	(6.0, 34.1)
		placebo	96			
754	US	400 mg	201	21.6%	0.0078	(6.3, 34.5)
		600 mg	97	24.6%	0.0061	(7.8, 38.3)
		placebo	104			
755	Europe, Australia	200 mg	160	14.4%	0.0223	(2.2, 25.1)
		400 mg	158	15.0%	0.0325	(1.4, 26.8)
		placebo	159			

For the 3 studies, subjects had a mean duration of epilepsy of 24 years and a median baseline seizure frequency ranging from 10–17 per 28 days. Eighty-four percent (84%) of subjects were taking 2 to 3 concomitant antiepileptic drugs, with or without concurrent vagal nerve stimulation.

All 3 studies showed a fairly robust treatment effect that survived sensitivity analyses and different imputation paradigms for missing data. The results were also positive if seizures that occurred during the Titration Phase were considered in the analyses. Study 667 (but not 755) provided evidence in favor of greater efficacy of the 400-mg daily dose versus the 200-mg daily dose; however, both studies that included a 600-mg daily dose (667 and 754) failed to show that the 600-mg daily dose was more efficacious than the 400-mg daily dose. In all 3 studies, there was a clear dose response for adverse events, as well as for discontinuations for adverse events.

b(4)

Safety: I agree with the Division's conclusions regarding safety of lacosamide, with one slight exception. In the controlled studies in the epilepsy patient population, 2 lacosamide-treated subjects and 1 placebo-treated subject experienced syncope. The Division had a tendency to consider these 3 events in isolation, and declare that there was no signal for syncope in the epilepsy patient population. However, a total of 36 lacosamide-treated subjects experienced syncope in phase 2 and 3 studies in all indications, compared to only 2 placebo-treated subjects. In open-label epilepsy studies, an additional 8 subjects experienced an episode of syncope; 2 had received 400 mg/day, and the remainder had received ≥ 500 mg/day. In Phase 1 studies, 4 subjects (all on lacosamide) experienced syncope. Thus, it is appropriate that the labeling include a warning/precaution for syncope. Although the risk may be lower in patients with epilepsy than in patients with diabetic neuropathy (the latter may have dysautonomia and cardiovascular disease, and have concomitant use of multiple cardiovascular medications), the risk should not be minimized in the epilepsy population.

The sponsor has agreed to conduct an *in vitro* postmarketing study to determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19.

Abuse and Dependence

According to Dr. Bonson of CSS, in a human abuse study in subjects with a history of abuse of CNS active agents, 200-800 mg lacosamide produced subjective responses on visual analogue scales of drug liking that were different from placebo and similar (at the 800 mg dose) to alprazolam, a Schedule IV drug. Further, there were reports of euphoria in Phase 1 studies in healthy volunteers, as well as a high rate of "feeling drunk" in another Phase 1 study in healthy individuals. For these reasons, CSS has recommended that lacosamide be scheduled in Schedule IV of the Controlled Substances Act.

As noted by Dr. Katz, "...the sponsor continues to disagree with CSS's recommendation that lacosamide be placed in Schedule IV of the CSA. The sponsor has, in effect, appealed this recommendation, and has had a telephone conference with Dr. Doug Throckmorton, Deputy Director of CDER, and staff of DNP and CSS to discuss this. Subsequent to this conference, the sponsor has submitted additional data requested by Dr. Throckmorton, who will be reviewing it. Clearly, a decision about scheduling will not have been made by the PDUFA date (today). Nonetheless, we recommend that these applications be approved today, and we have come to an agreement with the sponsor on language for labeling describing the data addressing abuse potential. It is important to point out that, by signing FDA form 356H, the sponsor has agreed to not market the product until a final decision on scheduling has been made." The Approval letter will remind the sponsor of their commitment in this matter.

NDA 22-254

I also agree with the Division's recommendation to approve [redacted] for use of lacosamide intravenous injection for the treatment of partial seizures in adults with epilepsy, based on a finding of bioequivalence between a 200-mg dose of the infusion given as a 30 or 60 minute infusion and 2 X 100-mg tablets in 27 healthy volunteers (study 658).

The safety of the IV formulation was demonstrated in approximately 200 subjects who received intravenous infusions of lacosamide as replacement for their oral doses (same dosing regimen and daily dose as their oral dose) for 2-5 days. In study 757, 160 subjects received ≥ 5 days of IV lacosamide infused over 10 (n=20), 15 (n=100), or 30 (n=40) minutes. All subjects received ≥200 mg/day, and 65 subjects received daily doses of ≥400 mg given over 15 minutes. A total of 32 subjects received doses of ≥ 400 mg/day given over 30 minutes. No new or concerning adverse events were observed.

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[redacted]

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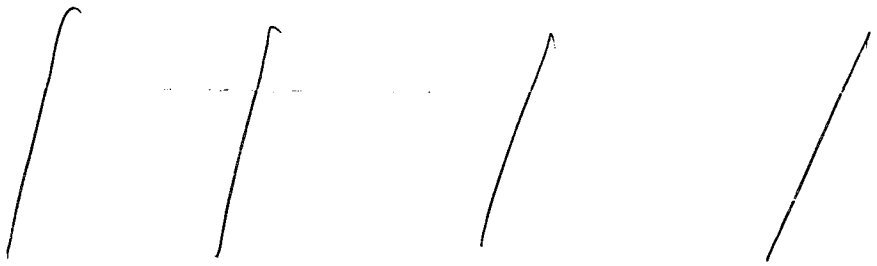


Pharmacology/Toxicology

There are no pharmacology issues that would preclude approval. However, adverse effects on neurodevelopment observed in a juvenile rat study, as well as a suggestion of effects on learning and memory in the offspring in the pre-and post-natal development rat study, argue for further evaluation of this finding in a non-clinical study. All agree that this can be performed post-marketing.

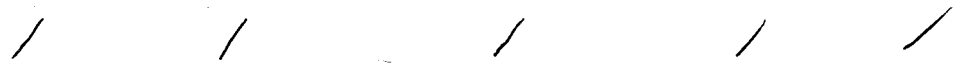
Conclusions and Recommendations

I concur with the Division's recommendation to approve NDAs 22-253 and 22-254, with attached labeling. The sponsor has submitted adequate evidence of safety and substantial evidence of effectiveness for the use of lacosamide oral tablets as adjunctive treatment for partial seizures in adults with epilepsy. They have also demonstrated bioequivalence of the intravenous solution of lacosamide to lacosamide oral tablets, when given as either a 30 or 60 minute infusion. There is some evidence of dose response between 200 and 400 mg/day, but no appreciable increment in effectiveness with 600 mg/day, despite a considerable increase in adverse events. Therefore, the recommended dose range will be 200-400 mg/day, given in a BID regimen. Under these circumstances, it is appropriate to display the adverse events in the 600-mg treatment group in labeling, and this is planned.

Labeling will include the new class warning regarding an increased risk of suicidal thoughts and behaviors (as recommended by the PCNS Advisory Committee). Labeling will also include prominent language regarding dizziness and ataxia, PR prolongation, and syncope, as particular issues of concern. Labeling will also include a new class Medication Guide.

There will be Phase 4 commitments for the sponsor to study brain changes in developing rats, with drug given throughout the period corresponding to the relevant period in human development, as well as an *in vitro* study to determine which enzymes, in addition to CYP2C19, may be involved in the metabolism of lacosamide. Furthermore, the Division will require that the sponsor perform adequate trials in pediatric patients with partial seizures from the ages of 1 month to 16 years of age as a Post Marketing Requirement (as with other AEDs initially approved in adults).

b(4)



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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ellis Unger
10/28/2008 06:12:15 PM
MEDICAL OFFICER

MEMORANDUM

DATE: October 28, 2008

FROM: Director
Division of Neurology Products/HFD-120 b(4)

TO: File, NDA 22-253, 22-254

SUBJECT: Recommendation for action on NDAs -253, 22-254, — for the use of VIMPAT (lacosamide) tablets, solution, and injection, respectively, as adjunctive treatment for partial seizures in adult patients with epilepsy. b(4)

NDAs 22-253, 22-254, —, for the use of VIMPAT (lacosamide) tablets, solution, and injection, respectively, as adjunctive treatment for partial seizures in adult patients with epilepsy, were submitted by Schwarz Biosciences on 9/28/07. Essentially all of the safety and effectiveness data were generated with the tablet dosage form (NDA 22-253), with the NDAs for the — intravenous injection relying on bioequivalence to the tablet formulation. b(4)

NDA 22-253 contains reports of three adequate and well-controlled studies (Studies 667, 754, and 755) in adult patients with partial seizures in which lacosamide was given as adjunctive therapy. In addition, the requisite safety, CMC, and non-clinical data were submitted. Because initial review of the application revealed the capacity of lacosamide to cause a multi-organ hypersensitivity syndrome that the sponsor had not adequately investigated, we asked the sponsor to submit more detailed analyses of this issue. This analysis was submitted on 7/16/08, and resulted in an extension of the PDUFA goal date. At the same time that the — NDAs referred to here were submitted, the sponsor also submitted NDA —for the use of lacosamide in the treatment of the pain of diabetic peripheral neuropathy, to the Division of Analgesic, Anesthetic, and Rheumatology Products. That application was Not Approved, b(4)

These NDAs have been reviewed by Dr. Lourdes Villalba, safety reviewer, Dr. Sally Yasuda, Safety Team Leader, Dr. Tristan Massie, statistician, Drs. Vaneeta Tandon, Lei Zhang, Emmanuel Fadiran, and Hao Zhu, Office of Clinical Pharmacology, Drs. BeLinda Hayes and Ed Fisher, pharmacologists, Dr. Lois Freed, Pharmacology Team Leader, Dr. Paul Brown, ODE Associate Director for Pharmacology and Toxicology, Drs. Wendy Wilson and Prufull Shiroman, chemists, Dr. Stephen Grant, cardiology reviewer, Dr. Katherine Bonson, Controlled Substance Staff, Dr. Ling Chen, statistician, Dr. Judy Park, Division of Medication Errors, Dr. Sheryl Gunther, Division of Scientific Investigations, and Dr. Norman Hershkowitz, Neurology Team Leader. The review team recommends that lacosamide oral tablets and intravenous injection be approved for use as adjunctive treatment for partial seizures in adults with epilepsy.

b(4)

In this memo, I will briefly review the relevant effectiveness and safety data submitted in support of the epilepsy indication, and offer the division's recommendation for action on these — NDAs. b(4)

EFFECTIVENESS

As noted above, the sponsor submitted reports of three adequate and well-controlled trials in support of the proposed claim for the use of lacosamide as adjunctive treatment for partial seizures in adults with epilepsy. I will briefly review the results of these trials.

Study 667

This was a randomized, multi-center (US and Europe), double-blind, parallel group trial in which patients being treated with 1 or 2 anti-epileptic drugs (AEDs) were randomized to receive either lacosamide 200 mg/day, 400 mg/day, 600 mg/day, or placebo, given Q 12 Hours. After an 8 week Baseline Phase, in which patients were required to have an average of at least 4 seizures/4 weeks, patients were entered into a 6 week titration phase, then a 12 week Maintenance Phase. Patients entering an open-label extension then entered a 2 week Transition Phase; those choosing not to continue were withdrawn from drug over 3 weeks.

The primary outcome measure was Reduction From Baseline in 4 Week Seizure Frequency During the Maintenance Phase, analyzed by an ANCOVA with terms for treatment and region, based on log transformed seizure frequency, with log-transformed average baseline seizure frequency as the covariate. Testing was to be hierarchical, with the highest dose tested first and mid-and low-doses tested sequentially.

Secondary outcome measures were proportion of responders (those with at least a 50% decrease in seizure frequency compared to baseline), reduction in seizure frequency for the entire treatment phase, seizure-free status, Clinical Global Impression of Change, and many others.

Results

A total of 421 patients were randomized, and a total of 418 had at least one post-baseline efficacy evaluation. A total of 347 patients completed titration, 321 (77%) completed maintenance, and 312 (75%) completed the entire trial. Discontinuations due to adverse events were clearly dose-related. The following percentage of discontinuations for adverse events by dose are described below:

Percent Discontinuations for Adverse Events by Dose

Placebo	5%
200 mg/day	15%
400 mg/day	19%
600 mg/day	30%

The following results on the primary outcome measure, derived by Dr. Massie, are described:

Median Percent Reduction in Seizure Frequency Compared to Placebo

Dose	N		P-value vs Pbo
200 mg/day	107	-14.8%	0.14
400 mg/day	107	-27.9%	0.003
600 mg/day	105	-21.5%	0.026

In general, the results were comparable across multiple analyses using different imputation schemes for missing data. If all seizures were counted, including those that occurred during the Titration Phase, the corresponding percent changes from baseline compared to placebo were about 7%, 20%, and 28% for the 200, 400, and 600 mg/day doses, respectively. The differences in proportion of responders compared to placebo were 12%, 19%, and 16% for the 200, 400, and 600 mg/day doses, respectively.

Study 754

This was of similar design as Study 667, except there were only 3 groups (placebo, 400, and 600 mg/day) and the study was performed entirely in the US.

Results

A total of 405 patients were randomized, and all received at least one dose and had at least one effectiveness assessment. Discontinuations due to adverse events were again dose related (5%, 18%, and 27% for placebo, 400, and 600 mg/day groups, respectively).

The results of the analyses of the primary outcome, performed by Dr. Massie, are given below:

Median Percent Reduction in Seizure Frequency Compared to Placebo

Dose	N		P-value vs Pbo
400 mg/day	201	-21.2%	0.011
600 mg/day	97	-24.8%	0.009

In general, the results were similar regardless of imputation methods used for missing data. If all seizures are included (not just those during Maintenance), the corresponding reductions from baseline compared to placebo are 12.8% and 11.7% for the 400 and 600 mg/day groups, respectively. The differences in responder rate compared to placebo were 21% and 23% for the 400 and 600 mg/day groups, respectively.

Study 755

This was a study of similar design as the two previously described studies, except there were 3 arms (placebo, 200 mg/day, and 400 mg/day), the study was performed in Europe and Australia, and there was a 4 week (as opposed to a 6 week) Titration Phase.

Results

A total of 485 patients were randomized, and all 485 received at least one dose and had at least one effectiveness evaluation. Discontinuations due to adverse events were dose related, with 5.5%, 6%, and 16% discontinuing for adverse events in the placebo, 200, and 400 mg/day groups, respectively.

The following analyses, performed by Dr. Massie, are presented:

Median Percent Reduction in Seizure Frequency Compared to Placebo

Dose	N		P-value vs Pbo
200 mg/day	160	-13.6%	0.05
400 mg/day	158	-27.3%	0.027

In general, the results were similar regardless of imputation methods used for missing data. If all seizures are included (not just those during Maintenance), the corresponding reductions from baseline compared to placebo are 11.4% and 15% for the 200 and 400 mg/day groups, respectively. The differences in responder rate compared to placebo were 9% and 15% for the 400 and 600 mg/day groups, respectively.

SAFETY

A total of 944 patients were randomized to lacosamide oral tablets in controlled trials of patients with epilepsy. A total of 1327 patients with epilepsy were exposed to lacosamide in controlled and uncontrolled trials. In addition, a total of 644 healthy volunteers received at least one dose of an oral formulation of lacosamide in 21 Phase 1 studies (including pharmacokinetic, abuse liability, QT, drug interaction, and special population studies).

In epilepsy studies, a total of 1000 patients received lacosamide for at least 6 months (2163 patient-years), and 590 patients received lacosamide for at least 2 years (1704 patient-years).

A total of 133 patients received at least 400 mg/day for 6 months to 1 year. A total of 334 patients received at least 400 mg/day for 1-2 years.

Further, a total of 2001 patients with neuropathic conditions (1939 with painful diabetic neuropathy) were exposed to lacosamide. This memo will largely be restricted to a description of the safety in the epilepsy population, but, as with Dr. Villalba's review, I will also highlight those findings from the diabetic population where they differ from the findings in the epilepsy population.

Deaths

There was one death in a patient treated with lacosamide in controlled trials in epilepsy (a 63 year old man with a history of depression who committed suicide upon learning his wife was diagnosed with cancer; he had received 68 days of treatment and it was unclear if he had received drug in the preceding 3 weeks), and no deaths in placebo treated patients. There were 8 deaths in open-label treatment, 4 of which were consistent with Sudden Unexplained Death in Epilepsy (SUDEP). As noted by Dr. Villalba, this yields a SUDEP rate of .002 deaths/patient-year, a rate consistent with that with other AEDs. None of the other deaths were reasonably attributable to drug (see Dr. Villalba's review, Table 6, pages 23-25).

In the diabetic population, there were 4 deaths in controlled trials (out of 1023 lacosamide treated patients), and 11 additional deaths in open-label treatment, and no deaths in placebo-treated patients. A total of 8 deaths were related to cardiovascular events (3 in controlled trials; v. fib, MI, heart failure, myocarditis, cardiac arrest, and sudden death). All of these patients had pre-existing cardiovascular disease. The other deaths were unlikely related to drug (including 5 cancers, all of different type).

The mortality in all controlled trials (regardless of indication) was 0.3% in lacosamide-treated patients (5/1967) and 0% in placebo-treated patients.

Serious Adverse Events

In epilepsy controlled trials, the rate of SAEs was 6.5% in lacosamide- and 3.8% in placebo-treated patients. There was no dose-response for SAEs.

The most common SAEs were Nervous System disorders (2.1% vs 1.6% in placebo), Psychiatric disorders (0.7% vs 0% in placebo), and Gastrointestinal disorders (0.6% vs 0.3% in placebo). In the Nervous System category, seizures of various type were the most frequently reported, but not at a rate greater than in the placebo group. The most frequent SAE in the Nervous System category was Dizziness, in 3/203 patients treated with 600 mg/day, compared to 0/364 placebo treated patients.

In the Psychiatric disorders group, there was no SAE that occurred in more than one patient, except Psychotic Disorder, which occurred in 2/471 patients treated with lacosamide 400 mg/day, compared to 0/364 placebo-treated patients. In only one of these patients was the psychosis considered treatment related (52 year old man with a history of depression, delusional disorder, panic attacks, and psychotic disorder [all poorly documented], who behaved "strangely" after 11 days at 400 mg/day). Twenty days after treatment discontinuation, the behaviors were not resolved.

No GI SAEs were of concern.

In open-label treatment, no additional particularly important events were considered to have been related to treatment, save for the following.

A 30 year old man experienced several episodes of dizziness ½-1 hour after various lacosamide doses (400-1000 mg/day). Twelve days after discontinuing treatment, he developed nausea, abdominal discomfort, fatigue, and brown urine. Three days after this, his AST was 1550 U/L, ALT 422 U/L, gamma-GT 982 U/L, proteinuria and casts. Bilirubin was not measured at that time, but several days later was normal, when the AST and ALT were markedly improved. Tests for viral hepatitis were normal.

There was a patient with hallucinations in the epilepsy trials, but that patient was also taking recreational psychoactive drugs (amphetamine, marijuana). Another patient who received 600 mg/day for 2 days (he had been titrated to this dose) in a study of an oral capsule developed visual hallucinations. He was treated with IV lorazepam, his dose was dropped to 400 mg/day, and he recovered.

In the diabetic population, most of the SAEs were Cardiac disorders (angina, coronary artery disease, a. fib., a. flutter., bradycardia). Although the frequency of cardiac SAEs were the same between drug and placebo (2.5-2.9%), most of the conduction/rhythm abnormalities were in the drug-treated group. Of particular concern was the frequency of syncope in this population (7.3% on drug

vs 2.4% in placebo-treated patients). A total of 0.5% (5/1023) lacosamide-treated patients discontinued treatment in controlled trials compared to 0 placebo patients due to syncope. Most of these cases were not monitored with EKG; in the few that were, those with apparent cardiac etiology were seen at a dose of 600 mg/day.

Discontinuations due to Adverse Events

A total of 17% of lacosamide-treated patients discontinued controlled trials in epilepsy, compared to 5% of placebo-treated patients. These were clearly dose-related, as seen below:

Placebo	4.9%
200 mg/day	8.1%
400 mg/day	17.2%
600 mg/day	28.6%

Almost all of the events reported by System Organ Class (SOC) that resulted in treatment discontinuation were dose related (see Dr. Villalba's Table 19, pages 47-8). The most common SOCs in which discontinuations occurred were Nervous System (9.9% vs 2.5% in placebo), GI (3.2% vs 0.8%), Eye Disorders (3% vs 0.3%), General (1.7% vs 0.3%), Psychiatric (1.6% vs 0%), and Ear and Labyrinth Disorders (1.4% vs 0%), and almost all of these were dose-related.

The following table displays those events that resulted in treatment-discontinuation, were dose related, and for which the frequency in the 600 mg/day dose was greater than 1%:

Event	Pbo	200 mg/d	400 mg/d	600 mg/d
Dizziness	.6%	0.4%	4.2%	17.2%
Coordination Abn'l (Ataxia)	0%	0.4%	1.3%	5.4%
Nausea	.3%	0.4%	1.7%	3.9%
Vomiting	.8%	0.4%	2.3%	3.0%
Blurred Vision	0%	0.4%	0.6%	3.0%
Tremor	0%	0%	0.6%	2.5%
Nystagmus	0%	0%	0.2%	2.5%
Diplopia	.3%	1.5%	2.1%	2.0%
Asthenia	0%	0%	0%	2.0%
Fatigue	.3%	0%	0.7%	1.5%

Additional patients had their dose of lacosamide decreased due to adverse events (see Dr. Villalba's Table 27, page 58). Similar events as those resulting in

treatment-discontinuation in the controlled trials in epilepsy also resulted in treatment discontinuation in the open-label epilepsy studies (see Dr. Villalba's Table 28, page 59 and Table 29, page 61).

Common Adverse Events

In controlled trials in epilepsy, a total of 81% of lacosamide-treated patients experienced at least one adverse event compared to 65% of placebo-treated patients. Overall adverse events were dose related; those adverse events previously seen to be dose related and considered as serious or that led to discontinuation and described above were also dose related when the total frequency were considered (see Dr. Villalba's Table 58, page 108).

In the diabetic population, the most common adverse events were also in the Nervous System, with the most common being Dizziness, occurring at a frequency of 83% in the 600 mg/day group.

Laboratory Measures

There were no systematic changes in mean hematologic parameters or routine chemistries, including liver function tests. There were no systematic increases in the proportion of patients developing clinically important changes in hematologic parameters, or in routine clinical chemistries.

Vital Signs

There were no systematic changes in mean blood pressure or pulse rate during the controlled trials in epilepsy. There was a slight increase in the proportion of patients who met outlier criteria at least once for changes in blood pressure at the 600 mg/day dose compared to placebo as below:

SBP Increase of at least 20 mm Hg
Pbo 22.5%
600 mm Hg 29.1%

	DBP Increase of at least 10 mm Hg	DBP Increase of at least 20
Pbo	39.2%	7.8%
600 mm Hg	48.8%	12.3%

Most of these changes occurred once (see Dr. Villalba's Table 69, page 125 for further details).

EKG

There was a dose related increase in mean PR interval in the controlled trials in epilepsy, as follows:

Mean Change From Baseline in PR Interval (msec)

Placebo	-0.3
200 mg/day	1.4
400 mg/day	4.4
600 mg/day	6.6

A similar pattern of increase in mean PR interval was seen in Study 640, a thorough QT study. In that study, the maximum mean changes in PR interval on Day 6 were seen at 1 hour post-dose, and were 6.3, 13.6, and 18.2 msec in the placebo, 400, and 800 mg/day groups, respectively. In addition, at Tmax on Day 6, there was a mean shortening of the QT interval of 9.4 msec compared to placebo at the 400 mg dose, and of 7.4 msec at the 800 mg dose. There were no important mean changes in other EKG parameters in either the controlled trials or in Study 640.

There was a slight increase in the proportion of patients treated with lacosamide that had at least one documented episode of PR increase of greater than 200 ms (8.8%) compared to placebo (4.5%), but this was not dose related. There was also a slight increase in the proportion of patients who had at least one episode of QRS duration greater than 120 ms on lacosamide (2.6% and 3.5% on 400 and 600 mg/day, respectively) compared to placebo (1.4%).

In Study 640, the following percent of patients had the described increase in PR interval in msec on Day 6:

Dose	At least 200	At least 220	At least 250
Placebo	0	0	0
400 mg/day	1.8%	1.8%	0
800 mg/day	13.5%	5.8%	1.9%

There were no other important changes in EKG parameters seen in Study 640.

In two of the controlled trials in epilepsy (Studies 744 and 745), a common central EKG reader was used. In these studies combined, the percentage of patients with a broad QRS was 3% in the placebo group and 12% in the 600 mg/day group.

A thorough QT study (Study 640) was performed at doses of placebo, 400 and 800 mg/day. In this study, there were mean changes as follows at Day 6 (end of treatment):

Mean Changes From Baseline at Day 6

	Placebo (N=55)	400 mg/day (N=57)	800 mg/day (N=56)
SBP (mm Hg)	-2.5	1.9	8.6
DBP (mm Hg)	2.0	3.9	10.3
Pulse (BPM)	-6	-1	2.7

There were no systematic changes in the proportion of patients who met criteria for orthostatic blood pressure or pulse changes in this study.

Adverse Events of Special Interest

Syncope

There were a total of 36 lacosamide-treated patients who experienced an episode of syncope in Phase 2/3 studies in all indications, compared to 2 placebo-treated patients. In the epilepsy controlled studies, 2 lacosamide and 1 placebo-treated patient experience syncope. In open-label epilepsy studies, an additional 8 patients had an episode of syncope; 2 were at 400 mg/day, and the rest were receiving at least 500 mg/day. In Phase 1 studies, 4 subjects (all on lacosamide) experienced syncope.

In the diabetes controlled trials, 13 lacosamide-treated patients experienced syncope compared to 0 placebo-treated patients; 11 were receiving 600 mg/day. Thirteen more patients experienced syncope in the open-label experience; 10 discontinued treatment as a result. Of these latter 13, the sponsor considered 3 to have been related to cardiac causes (one patient had a. flutter and tachycardia, and one was considered to have had first degree AV block, intermittent second degree AV block, and bradycardia).

Liver Injury

There were few patients who developed significantly abnormal LFTs, as noted above. In epilepsy controlled studies, 4 patients randomized to lacosamide met LFT outlier criteria for withdrawal (see Dr. Villalba's Table 45, page 90, for specific criteria), although one was receiving placebo at the time. Two of the withdrawn patients resolved off treatment, but one patient was lost to follow-up.

In one patient, the ALT reached at least 10 X ULN (as did a placebo patient), and in one case the elevated LFTs were confounded by acute alcohol use. Bilirubin levels were never abnormal.

Cognitive/Memory Impairment

Although poorly described, the following frequencies of related events in the controlled epilepsy studies is given below:

Event	Pbo (N=364)	200 m/d (N=270)	400 m/d (N=471)	600 m/d (N=203)
Amnesia	0.5%	0	0.4%	1%
Cognitive Disorder	0.3%	0.4%	2.1%	2%
Attention Disorder	0.5%	0	1.5%	2.5%
Memory Impairment	1.9%	0.4%	1.5%	5.9%
Mental Impairment	0	0	0.4%	1%

Suicidal Ideation and Behavior

A meta-analysis of 199 controlled trials of 11 marketed AEDs (not including lacosamide) across numerous indications has recently been performed that revealed an elevated risk of suicidal ideation and behavior across this class. This increased risk appears to be present regardless of indication, although the relative risks (though not the attributable risks) appear to vary by indication. The increase is seen for both ideation and behavior. As a result, the labeling for all AEDs, including those not included in the analyses (and including lacosamide) will be changed to include a prominent warning about this risk, and all AEDs will have Medication Guides.

In the lacosamide epilepsy trials, 0.3% (3/944) patients had such an event (one suicide, one ideation, and one suicide attempt) compared to 0 placebo-treated patients, as originally reported by the sponsor. When the sponsor was asked to perform an analysis of all of their controlled trials of at least 4 weeks duration of the sort done in the meta-analyses (which required a standardized search of the database using specific strings of search terms to identify potential cases, writing narratives of these cases, and then categorizing these potential cases according to a standardized classification system), the sponsor identified 6 such cases in lacosamide-treated patients, all in epilepsy controlled trials. Two of these patients were not receiving lacosamide at the time of the event. This yields a frequency of these events of 0.2% (4/2291 [0.4% in epilepsy trials]) compared to 0 placebo-treated patients.

Multi-organ hypersensitivity reactions

Several AEDs have been noted to be associated with a so-called multi-organ hypersensitivity syndrome. This reaction, also referred to as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), typically presents with fever, rash, lymphadenopathy, evidence of injury to several organ systems, and eosinophilia, although events are often considered to be cases of this syndrome that do not necessarily have all of these elements.

Because of the previously described case of hepatitis and nephritis, we asked the sponsor to examine the database for additional possible cases of this syndrome. The details of the methodology of the search are described in Dr. Villalba's review of 9/26/08. Ultimately, in addition to the case previously described, several other cases were considered potential cases.

One was a 27 year old man who received 7 days of drug a mild forearm rash and very slight elevations of LFTs, both of which resolved 5-7 days after discontinuing drug.

A 77 year old man with diabetic neuropathy was treated for 30 days, taken off drug for about 2 months, and re-started for an additional 44 days, at which point he was noted to have a mild rash. Six days later, he had ALT/AST of about 300, GGT of 550 U/L (10 fold ULN), ALP of 141 U/L (ULN 119), and a bilirubin of 1.34 mg/dL, up from about .7 (ULN 1.1). Drug was discontinued three days later; the next day, the ALT was markedly improved (83), ALP 125, GGT 7X ULN, and bilirubin was normal. Eosinophils were 7.8% (ULN 6%).

One more case of interest was a 39 year old man with diabetic neuropathy who developed tachycardia after about 2 months on drug (110 BPM) that lasted about a month. He died about 5 months after the onset of the tachycardia, and 4 months after it was reported to have resolved. The patient's last prescription for drug was given about 3 months before his death, and the prescription was for a 3 month supply of drug, but there is no documentation of whether the patient continued to take drug up to the time of death or not.

At autopsy, he was noted to have myocarditis and "toxic" damage to the liver. The sponsor notes that the patient was "suffering from alcoholic intoxication" at the time of death, although there is no independent history of alcohol use or abuse.

Abuse and Dependence

According to Dr. Bonson of CSS, in a human abuse study in subjects with a history of abuse of CNS active agents, 200-800 mg lacosamide produced subjective responses on visual analogue scales of drug liking that were different from placebo and similar (at the 800 mg dose) to alprazolam, a Schedule IV

drug. Further, there were reports of euphoria in Phase 1 studies in healthy volunteers, as well as a high rate of "feeling drunk" in another Phase 1 study in healthy individuals. For these reasons, CSS has recommended that lacosamide be scheduled in Schedule IV of the Controlled Substances Act. At the time of this writing, the sponsor h

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NDA 22-255

As noted above, the sponsor has submitted NDA 22-255, for the use of lacosamide intravenous injection for the treatment of partial seizures in adults with epilepsy. The basis for a finding of safety and effectiveness for this formulation is a finding of bioequivalence between a 200 mg dose of the infusion given as a 30 or 60 minute infusion and 2 X 100 mg tablets in 27 healthy volunteers.

Specifically, the following measures of bioequivalence were seen in Study 658:

	Cmax		AUC	
	Pt Estimate	90% CI	Pt Estimate	90% CI
Solution/tablet 30 min infusion	1.15	(1.07, 1.22)	1.00	(0.98, 1.01)
Solution/tablet 60 min infusion	1.03	(0.96, 1.10)	1.00	(0.98, 1.02)

The Tmax's were 0.5, 1, and 0.75 hours for the 30 minute infusion, 60 minute infusion, and the oral tablet, respectively. Cmin's were comparable between 30 minute infusion and tablet (Cmin for the 60 minute infusions was not presented).

Approximately 200 patients received intravenous infusions of lacosamide as replacement for their oral doses (same dosing regimen and daily dose as their oral dose) for between 2 and 5 days. In one study, Study 757, a total of 160 patients received up to 5 days of IV lacosamide at infusion rates of either 10 (N=20), 15 (N=100), or 30 (N=40) minutes. All patients received at least 200 mg/day, and a total of 65 patients received daily doses of at least 400 mg given over 15 minutes. A total of 32 patients received doses of at least 400 mg/day given over 30 minutes. No new or worrisome adverse events were seen, save for a 48 year old man receiving a beta blocker who experienced marked bradycardia (heart rate as low as 26 bpm) 7 minutes into a 15 minute infusion of 150 mg lacosamide. The event resolved after drug discontinuation. The sponsor concludes that this event was consistent with a vaso-vagal episode, although a

cardiac cause was considered, and could not, and cannot, definitively be ruled out. It should be noted that giving lacosamide over 15 minutes was found to fail bioequivalence criteria compared to the tablet, secondary to an elevated Cmax. The occurrence of this case of bradycardia suggests that this more rapid infusion may potentially be problematic, and together with the elevated Cmax (compared to the tablet),

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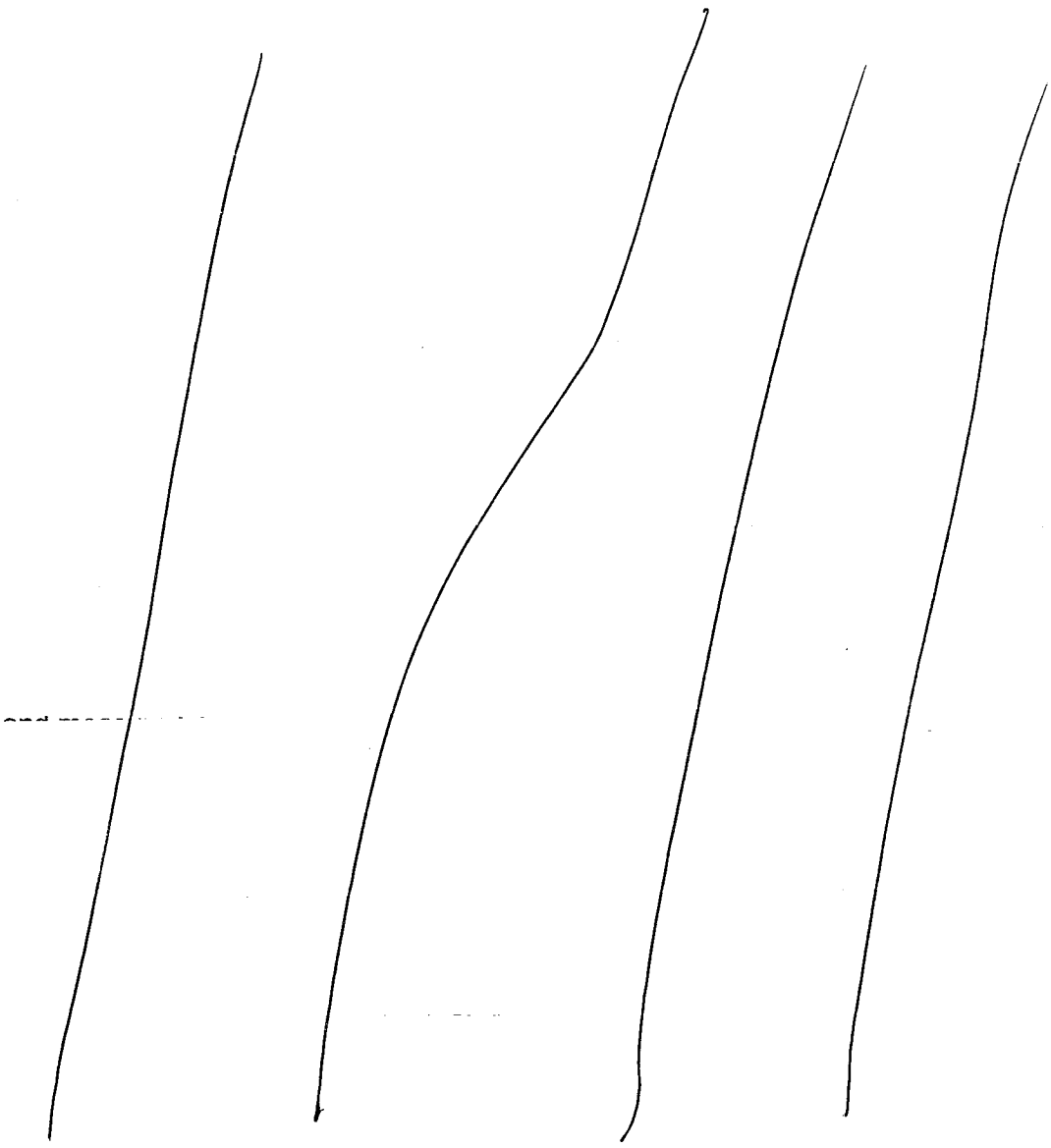

Pharmacology/Toxicology

There are no pharmacology issues that would preclude approval. However, as Drs. Fisher and Freed note, adverse effects on neurodevelopment seen in a juvenile rat study, as well as a suggestion of effects on learning and memory in the offspring in the pre-and post-natal development rat study argue for further evaluation of this finding in a well-designed non-clinical study that all agree can be done in Phase 4.

Conclusions and Recommendations

The sponsor has submitted adequate evidence of safety and substantial evidence of effectiveness for the use of lacosamide oral tablets as adjunctive treatment for partial seizures in adults with epilepsy. Further, they have shown the intravenous solution of lacosamide to be bioequivalent to lacosamide oral tablets, when given as either a 30 or 60 minute infusion. As several reviewers have noted, there is some evidence of dose response between 200 and 400 mg/day, but no appreciable increase in effectiveness with 600 mg/day, with a considerable increase in the incidence of adverse reactions at the latter dose. Therefore, the recommended dose range will be 200-400 mg/day, given in a BID regimen.

There are no unacceptable risks associated with the use of this product. Adverse events associated with the use of lacosamide, as described above, can be adequately described in labeling.

Specifically, labeling will include language, including in the Warning section, related to an increased risk of suicidal thoughts and behaviors (which will be class labeling for the AEDs, and which was recommended by the PCNS Advisory Committee; there will also be a class Medication Guide). Labeling will also include prominent language about the occurrence of dizziness and ataxia, PR prolongation, multi-organ hypersensitivity, and syncope, as particular issues of concern. There will be a Phase 4 commitment for the sponsor to perform a study to further examine the brain changes in developing rat, with drug given throughout the period that corresponds to the relevant period of human development.

For the reasons cited, then, we recommend that NDAs 22-253 and 22-254, for the oral tablet and intravenous injection, respectively, be approved, with the attached labeling.

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It should be noted that the sponsor

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Clearly, a decision about scheduling will not have been made by the PDUFA date (today). Nonetheless, we recommend that these applications be approved today, and we have come to an agreement with the sponsor on language for labeling describing the data addressing abuse potential. It is important to point out that, by signing FDA form 356H, the sponsor has agreed to not market the product until a final decision on scheduling has been made. The attached Approval letter reminds the sponsor of their commitment in this matter.

Because lacosamide will be accompanied by a Medication Guide describing the risk of suicidal thoughts and behaviors (a Medication Guide that will ultimately be required of all chronically administered AEDs), this will constitute a REMS, and the Approval letter will make mention of the sponsor's obligations in this regard.

The sponsor has also agreed to several changes in the carton and container labels. The Approval letter will describe the specific changes to which they have agreed.

The sponsor has not studied lacosamide in pediatric patients with partial seizures. As with other AEDs initially studied in, and approved for, adults, we will require, as a Post Marketing Requirement, that the sponsor perform adequate trials in pediatric patients with partial seizures from the ages of 1 month to 16 years of age, and this will be addressed in the Approval letter.

As noted earlier, our pharmacology staff has recommended that the sponsor perform an adequate pre- and post-natal study to examine lacosamide's effects on CNS development; the attached Approval letter embodies this as a Post Marketing Requirement.

Finally, Dr. Tandon of the Office of Clinical Pharmacology has requested that the sponsor undertake additional efforts to further characterize the pathways responsible for the metabolism of lacosamide. The Approval letter includes this as a Post Marketing Commitment.

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/s/

Russell Katz
10/28/2008 05:21:59 PM
MEDICAL OFFICER