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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.

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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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