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APPLICATION NUMBER:
022416Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	11/8/2013
From	Ellis F. Unger, M.D. Director, Office of Drug Evaluation-1
Subject	Office Director Decisional Memo
NDA#	022416
Applicant Name	Sunovion Pharmaceuticals Inc.
Date of Submission	02/10/2013
PDUFA Goal Date (post-extension)	11/11/2013
Proprietary Name / Established (USAN) Name	APTIOM eslicarbazepine acetate
Dosage Forms / Strength	Tablets: 200, 400, 600, and 800 mg
Proposed Indication	Adjunctive treatment of partial-onset seizures
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
Regulatory Project Manager	Su-Lin Sun
Division Director	Eric Bastings
Cross-Discipline Team Leader Review	Norman Hershkowitz
Clinical Review	Teresa Podruchny
Safety Review	Mary Doi Sally U. Yasuda
Biopharmaceutics	Elsbeth Chikhale
Biostatistics Review	Xiang Ling; Ling Chen
Pharmacology Toxicology Review	Christopher D. Toscano; Lois Freed Paul C. Brown
Chemistry Manufacturing Controls (CMC) Review	Charles F. Jewell Ali AL Hakim
Clinical Pharmacology Review	Bei Yu; Hongshan Li; Veneeta Tandon Venkatesh A. Bhattaram; Yuxin Men
Controlled Substances Staff	Alicja Lerner
Office of Scientific Investigations	John Hoon Lee
Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DMEPA)	Julie V. Neshiewat; Ermias Zerislassie; Marcus Cato; Laurie A. Kelley
OSE (Division of Risk Management)	Yasmin Choudhry
OSE (Division of Pharmacovigilance I)	Monica Muñoz
Division of Medical Policy Programs (DMPP)	Sharon W. Williams
Office of Prescription Drug Promotion (OPDP)	Melinda McLawhorn
PeRC PREA Subcommittee	George E. Greeley
SEALD	Elizabeth Donohoe ; Eric Brodsky

Eslicarbazepine acetate belongs to the chemical family that includes the anticonvulsants carbamazepine and oxcarbazepine. Their anticonvulsant actions are thought to be mediated through blockade of the voltage-gated sodium channel. Eslicarbazepine can be considered a pro-drug; it is rapidly and almost completely metabolized to S-licarbazepine (eslicarbazepine), with small amounts of R-licarbazepine and oxcarbazepine produced as well. Both S-licarbazepine and R-licarbazepine are thought to possess the predominant sodium channel anticonvulsant activity of this drug. Oxcarbazepine is metabolized to the same active moieties, but in different proportions. Following administration of eslicarbazepine acetate, the proportion of S-licarbazepine to R-licarbazepine is 21:1, whereas this proportion is 4:1 following administration of oxcarbazepine.

The application under review is a complete response to NDA 22416 for eslicarbazepine acetate tablets, and the proposed indication is for use as adjunctive treatment of partial seizures.

The NDA was initially submitted March 30, 2009, and received a complete response action on April 30, 2010 because of serious data quality issues. Briefly, the applicant had submitted the results of three controlled studies (Studies 301, 302, and 303). Study 303 was not found to be in compliance with Good Clinical Practice (GCP) requirements when audited by the applicant. The applicant had audited 6 sites in Mexico, and found infractions, deviations, and omissions that were both profound and widespread. These included: inadequate or missing documentation of study enrollment criteria, admission of subjects who did not meet enrollment criteria, missing medical history charts, lack of drug accountability logs, discrepancies between source documents and case report forms, undated case report forms, missing start and stop dates for concomitant anti-epileptic drugs, lack of reporting for numbers of seizures, seizure diaries that were not reviewed until well after a visit, missing electrocardiograms, and potential adverse events described in the source documents that were not included in the CRFs.

Studies 301 and 302 had fewer problems than 303; however, they too had significant issues. DSI found a number of problems that were unusually important and widespread. DSI argued strongly that the data were not to be trusted, and provided an opinion of "no confidence."

At various stages of the review, Dr. Podruchny, the clinical reviewer, discovered various anomalies and inconsistencies in the data listings and tables of the application. When brought to the applicant's attention, some issues were found to be caused by misunderstandings, but in other cases, the applicant noted important errors that weakened the review team's confidence in the data.

Studies 301 and 302 had a similar randomized, parallel group, placebo-controlled designs. In both studies, patients with partial seizures were randomized to receive either placebo or eslicarbazepine 400 mg, 800 mg, or 1200 mg once a day. Patients were first entered into an 8-week baseline during which they received placebo. This was followed by a 2-week titration phase, a 12-week maintenance phase, and a 4-week taper period.

The primary outcome was seizure frequency standardized per 4 weeks. For each study, 3 types of analyses were described: maintenance data (using data from the maintenance period only), conservative (using the maximum seizure frequency during either the baseline or titration period), and non-conservative (carrying forward seizure frequency during the titration period).

Dr. Russell Katz, who was the Director, Division of Neurology Products at the time, noted that “on face, as the data are presented by the sponsor, it appears that eslicarbazepine is effective...However, because we cannot be confident that the data are reliable, we cannot independently reach this (or any) definitive conclusion.”

The Complete Response letter requested detailed information regarding the sponsor’s audit program, and an additional audit of clinical sites that enrolled subjects in these Studies 301 and 302 to provide assurance that the safety and efficacy data were reliable. The letter also suggested that the applicant conduct at least one more adequate and well controlled clinical trial.

The Complete Response letter also noted:

“the studies only required the participants to update their seizure diaries when they experienced a seizure. As a result, failure to record seizures (i.e., missing data) could not be differentiated from the absence of seizure. Therefore, a worst-case imputation of all missing data (not just missing diary cards) is not possible. This limited our evaluation of the robustness of the efficacy results. Moreover, we note that the extensive use of hardcodes, performed to correct data errors (based on blinded and unblinded reviews of data), further supports our concern regarding the marginal quality of data provided in this study.

The extensive problems described in the conduct of the studies as well as in the reporting of the data raise significant questions about the reliability of the data. The deficiencies in the presentation of the data in your application further complicated our ability to rely on, and have hampered our ability to independently review, the data.”

The applicant sent a response to the initial CR letter on August 31, 2012, but this was deemed incomplete. The Division refused to file the submission because of continued deficiencies related to the accuracy, reliability, and presentation of the data. For example, adverse events were identified that had not been included in the primary or analysis datasets; some specific adverse events were inappropriately reported or coded. Inconsistencies between the narratives and the datasets were also identified. Specific requests and recommendations regarding the presentation and analyses of safety data were also made in the “refuse to file” letter.

The applicant took corrective actions, and resubmitted a response to the Complete Response on February 10, 2013.

The applicant submitted updated analyses of Studies 301 and 302, as well as the results of a new controlled study (Study 304). The updated analyses excluded two sites from Study 301 (a total of 20 patients) because of a Good Clinical Practice violation, and included additional data from seizure diary pages that had been omitted from 7 patients in Study 301 and 1 patient in Study 302. “Event-based diaries” had been used in Studies 301 and 302 for patient-level reporting of seizures. Such diaries report the occurrence of seizures, but diaries from days with no seizures are not filled out and/or returned. It is difficult or impossible, therefore, to discriminate between days with no seizures and days for which data are missing; in either case, diaries are not returned. The applicant’s original analyses assumed that patients did not have seizures after the last reported event. In the updated analyses, the day of the last returned diary card was considered to be the last day on study.

Table 1 shows that efficacy results from Study 301 and 302 were consistent with the original analyses and support the efficacy of eslicarbazepine 800 mg and 1200 mg.

Dr. Ling, the statistical reviewer, also reviewed the new study conducted by the applicant (Study 304). Study 304 initially used event-based diaries, as in Studies 301 and 302, but at

Table 1: Results of Studies 301 and 302

	Placebo	ESL 400 mg	ESL 800 mg	ESL 1200 mg
Study 301				
N	95	91	88	87
LS mean (SE)	6.6 (0.54)	5.8 (0.48)	5.0 (0.43)	4.3 (0.38)
Adjusted p-value	-	0.4969	0.0468	0.0010
Study 302				
N	99	94	87	81
LS mean (SE)	8.6 (0.62)	8.1 (0.60)	6.2 (0.48)	6.6 (0.53)
Adjusted p-value	-	0.9043	0.0057	0.0424

Source: Table 31 of ISE.

the request of FDA, switched to “daily diaries” after about 30% of patients had been randomized. As the name implies, daily diaries are returned daily, irrespective of whether or not a patient had a seizure. They are preferred, therefore, because they allow discrimination between days with no seizures and missing data.

Results of Study 304 were generally consistent with those of Study 301 and 302. The 1200 mg dose was statistically significantly better than placebo ($p=0.004$), and the 800 mg dose trended positively, almost reaching statistical significance ($p = 0.058$). Of note, the applicant used a Bonferroni adjustment for the comparisons of the 800 mg and 1200 mg dose to placebo, which is highly conservative in this setting, because it fails to take the expected correlation of the two treatment groups into account, i.e., the method assumes that the treatment groups are independent. Using a more traditional step-down procedure for endpoints with some degree of correlation, the nominal p-value is 0.029 for the 800 mg dose.

Table 2 shows that when the “daily diaries” (DE) population is considered, the treatment effect remains marginally statistically significant for the 1200 mg dose. The effect size is also similar between the “daily” diaries and the “event-based” diaries populations, which suggest that the type of diary used in the study did not have an important effect on the results. Dr. Ling also conducted a number of sensitivity analyses, and they were supportive of the primary efficacy findings.

Table 2: Efficacy results in Study 304

	Placebo	ESL 800 mg	ESL 1200 mg
ITT population			
N ^a	212	200	184
LS mean (SE)	7.88 (0.49)	6.54 (0.41)	6.00 (0.40)
95% CI	[6.98, 8.90]	[5.77, 7.40]	[5.26, 6.84]
Log difference in LS mean		-0.18	-0.26
Unadjusted p-value		0.029	0.002
Adjusted p-value ^b		0.058	0.004
DE ITT population			
N ^a	154	137	136
LS mean (SE)	7.54 (0.54)	6.32 (0.48)	5.96 (0.46)
95% CI	[6.55, 8.68]	[5.44, 7.35]	[5.12, 6.94]
Log difference in LS mean		-0.17	-0.22
Unadjusted p-value		0.094	0.026
Adjusted p-value ^c		0.167	0.049

a Subjects who discontinued from the study during the titration period were not included.

b Bonferroni's procedure was used to calculate the p-values.

c Dunnett's procedure was used to calculate the p-values (assessed at 0.025 level).

Source: Table 19 & 20 of the CSR for Study 304, confirmed by the reviewer.

Dr. Ling considers the quality of efficacy data in Study 304 to be acceptable. She notes that she had found extensive use of “hard-codes” to correct data errors in the analysis datasets of Studies 301 and 302 in her review of the original NDA, suggesting questionable data quality. She did not find a similar problem in Study 304. Dr. Ling also discussed data quality issues with patients who used event-based diaries, but noted that “based on the review of the dataset and select CRFs, the problems noted above were not deemed common.” Dr. Ling provided a worst-case analysis in which event-based diary data were excluded. Statistical significance remained for the comparison of 1200 mg vs. placebo (adjusted p-value=0.049). In the end, Dr. Ling concludes that the data support efficacy.

Dr. Podruchny disagrees, and recommends a Complete Response action, because on a lack of confidence in the data integrity. She cited the previous OSI and review findings, the need for repeated information requests and clarification from the applicant, and the receipt of responses from the applicant in which all issues in a finite set of records needed to evaluate the response were not correctly identified (for Study 304). Dr. Lerner, the Controlled Substances Staff reviewer, has likewise expressed serious concerns about the quality and reviewability of the data.

No one on the review team would disagree with Drs. Podruchny and Lerner: data quality has been an ongoing problem with this NDA. The question is whether the data quality is so poor that it undercuts our confidence to the point that we believe we are unable to interpret the data.

In the review of the original submission, I agreed with the Division that the data appeared to show eslicarbazepine’s effectiveness, but that data quality issues precluded an approval action. As discussed above, however, reanalyses of Studies 301 and 302 confirm the positive results. Results from Study 304 provide substantiation of efficacy.

Dr. Podruchny argues that the p-values were not consistently positive. Studies 301 and 302 were positive for 800 and 1200 mg. Study 304 did not achieve statistical significance at the lower dose, but, as noted, above, the use of the Bonferroni method exacted a large penalty, which was unnecessary given that results in the two treatment arms would be expected to be correlated. I agree with Dr. Bastings, that the results summarized in Table 3 provide acceptable evidence of efficacy for both doses.

Table 3: Primary efficacy results, Studies 301, 302, and 304

LS mean (p value vs. placebo)	Study 301	Study 302	Study 304
placebo	6.6	8.6	7.88
800 mg	5.0 (p=0.047)	6.2 (p=0.006)	6.54 (0.058)
1200 mg	4.3 (p=0.001)	6.6 (p=0.042)	6.00 (0.004)

Study 301 appears to show a dose-response, whereas the other 2 studies do not.

The basis for the initial complete response action was dubious data quality. Dr. Podruchny expressed "...a lack of confidence in data integrity at this time and uncertainty that the processes in place to conduct and/or oversee the trials in a corrective manner and present accurate data functioned/function effectively. This opinion is supported by previous OSI and review findings, evidence of the need for repeated requests and clarification of/from the Sponsor for information in this 3rd submission cycle, and the recent receipt of response(s) from the Sponsor in which the Sponsor did not correctly identify all issues in a finite set of records needed to evaluate for the response (for study 304)."

Dr. Podruchny further states "This application has received a high level of scrutiny. However, this has largely been driven by the problems encountered in review(s) though there were Sponsor-identified GCP problems in the first cycle with a fourth phase 3 study that is not considered reliable. I recommend the Agency consider whether evaluation of data management reconciliation reports for critical parameters (such as the primary endpoint in the efficacy studies) could provide complementary information to OSI inspections and review findings to assist in determining the integrity of the primary (efficacy) data."

The first cycle CR letter asked the applicant to provide information about the BIAL’s QA audit program, and to provide assurance that the safety and efficacy data obtained from Study 301 and 302 were reliable. The Agency suggested an audit, which the applicant conducted and provided with this submission. Dr. John Lee, from OSI, reviewed the findings, and highlighted 5 major GCP categories: 1) informed consent; 2) subject eligibility; 3) subject randomization; 4) adverse event reporting; and 5) drug accountability. For Studies 301 and 302, the audit included the review of nearly all subject records not reviewed during the original audit in 2008 (prior to NDA submission). For Study 304, approximately three-fourths of subject records

were reviewed by the applicant at 88 clinical sites (39 in North America and 49 in the rest of the world), and at two CRO sites.

Dr. Lee concludes that “The data from Study 304 appear reliable based on direct inspectional findings. Data reliability for Studies 301 and 302 are less clear (with or without data from OAI sites), but the totality of findings (sponsor’s audit, FDA inspections, consistent study outcomes) nonetheless support the acceptability of these two older studies as well (acceptable overall data reliability), as secondary supplemental studies to the primary pivotal Study 304.”

I agree with Drs. Bastings, Ling and Hershkowitz that Studies 301, 302, and 304 provide adequate evidence of efficacy, and an adequate assessment of the risks. The results from Studies 301 and 302 have stood up to a thorough audit from the sponsor and FDA inspections. Study 304, which had a better oversight than the earlier studies, was also thoroughly audited, and confirms the efficacy findings that were observed in the first review cycle. In particular, the more reliable daily diaries confirm the findings observed with event-based diaries.

The dataset errors identified by Dr. Podruchny are not sufficient, in my opinion, to discredit the efficacy results of Study 304. Some errors in the efficacy datasets and analyses appear to have resulted from patients switching from one type of diary to another during the trial, and may have been identified because of the very high level of scrutiny given to the datasets review.

Conclusion:

I do not mean to minimize the concerns of Drs. Podruchny and Lerner with respect to data quality. The problems with data quality have been vexing, to say the least. Clearly, the applicant did not have adequate safeguards in place to ensure data quality. But Dr. Lee’s inspection and review has concluded that the data from Studies 301, 302, and 304 are acceptable. Importantly, the review team has never expressed any concern that the errors are in any way directional, i.e., that they favor a finding of efficacy for eslicarbazepine. If anything, as noted by Drs. Ling, Lee, Hershkowitz, and Bastings, the errors contribute “noise” – similarly to all treatment groups. As such, the noise would only serve to make detection of a treatment effect more difficult. It is possible, however, that such “noise” could decrease apparent differences in the rates of adverse events. But the safety data have been carefully scrutinized by Dr. Doi, and she seems satisfied that the data are representative.

Regulatory Action:

Although there is some dissention, the review team generally agrees that approval is the appropriate regulatory action. I agree, and will take an approval action today for eslicarbazepine for the adjunctive treatment of partial-onset seizures.

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/s/

SU-LIN SUN
11/08/2013

ELLIS F UNGER
11/08/2013