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*APPLICATION NUMBER:*  
**022416Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Eric Bastings
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	22,416
<b>Supplement #</b>	
<b>Applicant Name</b>	Sunovion Pharmaceuticals Inc.
<b>Date of Submission</b>	2/10/2013
<b>PDUFA Goal Date</b>	11/8/2013
<b>Proprietary Name / Established (USAN) Name</b>	Aption/eslicarbazepine acetate
<b>Dosage Forms / Strength</b>	200, 400, 600 and 800 mg
<b>Proposed Indication(s)</b>	Adjunctive treatment of Partial Onset Seizures
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Teresa Podruchny and Mary Doi
Statistical Review	Xiang Ling
Pharmacology Toxicology Review	Chris Toscano
CMC Review/OBP Review	Charles F. Jewell Jr.
Biopharmaceutics	Elsbeth Chikhale
Clinical Pharmacology Review	Bei Yu
CDTL Review	Norman Hershkowitz
OSE/DMEPA	Julie Neshiewat
OSE/DRISK	Yasmin Choudhry
CSS	Alicja Lerner

### 1. Introduction and Background

The application under review is a complete response to NDA 22,416, for eslicarbazepine acetate tablets, proposed for use as adjunctive treatment of partial seizures.

NDA 22,416 was first submitted on March 30, 2009. The original submission received a complete response action because of serious data quality issues. These issues were discussed by Dr. Russell Katz (division director) and Dr. Ellis Unger (office director, and signatory authority for this NDA) in their memos respectively signed on April 29, 2010, and April 30, 2010. Briefly, Dr. Katz describes that the sponsor had submitted the results of three controlled studies (Study 301, 302, and 303). However, because of deficiencies in the conduct of the study, the sponsor determined that Study 303 could not be used in support of the application. Dr. Katz notes that the clinical team recommended that this application not be approved, not

because the drug has not been shown to be effective or safe, but because of profound and extensive deficiencies in the conduct and documentation of the studies, as well in the presentation of the data in the application.

Table 1 and Table 2 show the efficacy findings in Study 301 and 302, as described by Dr. Katz. Study 301 and 302 had a similar randomized, parallel group, placebo-controlled design. 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. There was then a two-week titration phase, followed by a 12-week maintenance phase, and a 4-week taper period. The primary outcome was seizure frequency standardized per 4 weeks. For each study, three types of analyses are 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).

**Table 1: Study 301 results**

	Pla	400	800	1200
Maintenance				
N	99	97	93	92
LS Mean	6.8	6.1	5.1	4.6
P-value		0.55	0.013	0.0004
Conservative				
N	102	98	98	97
LS Mean	7.0	6.2	5.3	4.8
P-value		0.47	0.018	0.001
Non-conservative				
N	102	98	98	97
LS Mean	6.9	6.2	5.2	4.8
P-value		0.51	0.013	0.0007

**Table 2: Study 302 results**

	Pla	400	800	1200
Maintenance				
N	99	94	87	81
LS Mean	9.0	8.3	6.6	7.0
P-value		0.80	0.006	0.04
Conservative				
N	100	96	98	94
LS Mean	9.2	8.5	7.2	7.9
P-value		0.72	0.028	0.25
Non-conservative				
N	100	96	98	94
LS Mean	9.2	8.2	6.8	7.5
P-value		0.54	0.007	0.11

Dr. Katz noted in his memo that “on face, as the data are presented by the sponsor, it appears that eslicarbazepine is effective and that there are no adverse events that would preclude approval. However, because we cannot be confident that the data are reliable, we cannot independently reach this (or any) definitive conclusion.”

The complete response (CR) letter sent to the sponsor also commented on reports for audits of clinical investigators sites enrolling subjects in Studies 301, 302, and 303, and stated that “based on our review of these audit reports, we have determined that the audit reports disclosed significant GCP violations and noncompliance with commonly accepted good clinical practices and federal regulations.” The CR letter further stated that “importantly, such audit reports constituted only a fraction of the total subjects investigated, raising concerns regarding the remaining unaudited sites. Given the limited number of subject records examined at audited sites, we do not find the results of these audits to be sufficient in scope or detail to allow for adequate assessment of data reliability. These deficiencies, taken together, raise serious questions about the integrity of the data derived from these studies. Although we are asking you to submit responses to the requests below, we are not confident that you can provide all of the information requested, or, if you can, that the responses will adequately address all of our concerns. You should be aware that we are likely to request that you conduct at least one more controlled trial under acceptable and accepted clinical practices.”

The CR letter asked for information regarding the sponsor’s audit program (e.g., Quality Assurance [QA] audit plan, QA program with respect to oversight of CROs hired to monitor the sites, corrective actions taken, and list of all non-compliant sites), and assurance that safety and efficacy data obtained in Study 301 and 302 are reliable, by an additional audit of clinical sites that enrolled subjects in these studies.

The CR letter also noted that “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 sponsor sent a response to the initial CR letter on August 31, 2012, but this response was considered incomplete, and the team refused to file the submission, because of continued deficiencies related to the accuracy, reliability, and presentation of the data. Adverse events not included in the primary or analysis datasets were identified, and some specific adverse events were inappropriately reported or coded. Inconsistencies between narrative information and dataset information were also identified. Specific requests and recommendations regarding the presentation and analyses of safety data were also made in the “refuse to file” letter.

## **2. CMC/Device**

I concur with the conclusions reached by Dr. Jewell regarding the acceptability of manufacturing of the drug product and drug substance. Manufacturing site inspections were found acceptable. Stability testing supports an expiry of 24 months for the 200 mg tablets and 48 months for the 400-1200 mg tablets. There are no outstanding issues.

## **3. Nonclinical Pharmacology/Toxicology**

I concur with the conclusions reached by Dr. Toscano that there are no outstanding pharmacology/toxicology issues that preclude approval.

Dr. Toscano notes that given the inability of the sponsor to identify a NOAEL in the pivotal juvenile toxicology study conducted in dogs, it is not possible to determine the safety of eslicarbazepine in a pediatric population. Dr. Toscano believes that additional studies in juvenile animals will be required to support studies of eslicarbazepine in the pediatric population.

## **4. Clinical Pharmacology/Biopharmaceutics**

I concur with the conclusions reached by Dr. Yu and by Dr. Chikhale that there are no outstanding clinical pharmacology and biopharmaceutics issues that preclude approval. As discussed by Dr. Hershkowitz, concerns regarding the appropriateness of a biowaiver for the 200 mg tablet strength were addressed during the review cycle. In addition, the clinical pharmacology review notes that the extent of systemic exposure to eslicarbazepine was increased in patients with renal impairment. Therefore, dose adjustments will be recommended for these patients.

## **5. Clinical/Statistical-Efficacy**

As noted above, Dr. Katz, who was division director during the review of the original NDA, concluded that, on face, and based on the results from Study 301 and Study 302, eslicarbazepine is effective. However, he could not reach a final conclusion because of data reliability issues and inadequate presentation of the data. The first cycle action letter also stated that the sponsor may be required to conduct at least one more controlled trial.

In this response, the sponsor submitted the results of a new controlled study (Study 304), and provided updated analyses of Study 301 and 302. As noted by Dr. Ling, statistical reviewer, these new analyses resulted from the audit program conducted after the first cycle CR letter was issued. The new analyses excluded two sites (301-174 and 301-175, with a total of 20 patients) from Study 301, because of GCP violation, and included additional data from seizure diary pages that were omitted from the study database for seven patients in Study 301 and one

patient in Study 302. In addition, the method for calculating seizure frequency was slightly revised (using the last returned diary card date as end of study period, instead of using the end of the maintenance period for that patient); the issue is that Study 301 and 302 only used event-based diaries, and the original analyses assumed that patients did not have seizures after the last reported event; the uncertainty of that assumption was removed in the updated analyses.

Table 3 shows that efficacy results from Study 301 and 302 were consistent with the original analyses and support, on face, the efficacy of eslicarbazepine 800 mg and 1200 mg.

**Table 3: Updated analyses of Study 301 and Study 302 (copied from statistical review, page 18)**

	Placebo	ESL 400 mg	ESL 800 mg	ESL 1200 mg
<b>Study 301</b>				
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
<b>Study 302</b>				
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.

Dr. Ling also reviewed the new study conducted by the sponsor (Study 304). As discussed by Dr. Ling, Study 304 initially used event-based diaries, as was done in Study 301 and 302, but switched to daily diaries after about 30% of patients had been randomized (daily diaries are preferred by FDA, as they allow differentiating between missing data and “no seizure” days).

Table 4 shows that efficacy results in Study 304 were generally consistent with those of Study 301 and 302. The 1200 mg dose was statistically superior to placebo ( $p=0.004$ ), and the 800 mg dose trended strongly (adjusted p value = 0.058). Of note, the sponsor used a Bonferroni adjustment for the comparisons of the 800 mg and 1200 mg dose, which is not the preferred approach for analysis of two dose levels in a clinical trial, as a significant contrast for the low dose but not for the high dose raises clinical interpretability issues. Using a more traditional step down procedure, the nominal p value becomes 0.029 for the 800 mg dose.

Table 4 also shows that when the “daily diaries” (DE) population is considered, the contrast remains statistically marginally 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 a major impact on the results. Dr. Ling also conducted a number of sensitivity analyses, which support the primary efficacy findings.

**Table 4: Efficacy results in study 304 (copied from Dr. Ling’s review, table 4, page 12)**

	Placebo	ESL 800 mg	ESL 1200 mg
<b>ITT population</b>			
N <sup>a</sup>	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 <sup>b</sup>		0.058	0.004
<b>DE ITT population</b>			
N <sup>a</sup>	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 <sup>c</sup>		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 acceptable. She notes that she had found (in her review of the original NDA) extensive hard-codes used to correct data errors in the analysis datasets of Study 301 and Study 302, indicating questionable data quality. However, she did not find a similar problem in Study 304. Dr. Ling also discusses in her review (page 15-16) data quality issues with patients who used event-based diaries, but notes that “based on the review of the dataset and select CRFs, the problems noted above were not deemed common”. Dr. Ling also notes that, in a worst case analysis in which event-based diary data were excluded, statistical significance is maintained for the contrast of 1200 mg vs. placebo (adjusted p value=0.049). Dr. Ling concludes that the data support efficacy.

Dr. Podruchny disagrees, and recommends a complete response action. Dr. Podruchny notes that “to the degree that the data are reliable for efficacy evaluation, it is difficult for me to conclude that considered as a whole, there is adequate support for a specific dose”. Dr. Podruchny goes further to say that “specifically, the p values for the 800 mg and 1200 mg group are not consistently positive across the three trials. I think it is fair to say that that discretion can reasonably be exercised to conclude that a p value, for example, of 0.49 versus 0.51 is not that different, though one technically meets the 0.05 threshold. However, this becomes more opaque to me when the basis of the data generating the p-value still seems questionable.”

I will first discuss my opinion about whether, on face, efficacy has been established, and then discuss whether data quality issues continue to hamper a definitive conclusion from being made.

## Efficacy

Dr. Katz, in his first cycle division director memo, noted that “on face, as the data are presented by the sponsor, it appears that eslicarbazepine is effective”. As discussed above, reanalyses from Study 301 and 302 confirm the results that were reviewed by Dr. Katz. In addition, the results from Study 304 provide additional independent substantiation of efficacy. Dr. Podruchny argues that the p values were not consistently positive. While that is technically true (one out of six contrasts had an adjusted value of 0.058), I disagree that the observation undermines the overall findings, and believe that the results (as summarized in Table 5) provide ample independent substantiation of efficacy for both doses (again, data provided in the original submission already led to that conclusion, with the caveat of data quality and presentation issues, which I will address below).

**Table 5: Primary efficacy results**

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)

I also note that the treatment effect size was quite consistent across all three studies (see Table 6), and, in Study 304, similar in patients who used daily diaries or event-based diaries, which mitigates the data reliability concerns for event-based diaries, as used in Study 301 and 302. In addition, the treatment effect size (Table 6) is in the ballpark of that of approved antiepilepsy drugs (with the usual limitations of across-studies comparisons).

**Table 6: median percent reduction in seizure frequency effect size from baseline (drug minus placebo)**

	Study 301	Study 302	Study 304
800 mg	-21%	-26%	-15%
1200 mg	-23%	-22%	-20%

## Impact of data quality and presentation issues over efficacy findings

The primary basis for the initial complete response action was data quality and presentation issues. Dr. Podruchny expresses “a lack of confidence in the data and a lack of confidence that the processes in place to conduct and/or oversee the trials in a corrective manner and present accurate data functioned/function effectively as supported by evidence of the need for repeated requests of the sponsor for information and clarification 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”. Dr. Podruchny further states “I acknowledge this application has received a high level of scrutiny. However, this has largely been driven by the problems encountered in review. I recommend that the Agency consider (probably with OSI input) whether evaluation of data management reconciliation reports for critical parameters (such as the primary endpoint in the efficacy studies and perhaps

serious adverse events in large non -epilepsy studies) could provide complementary information to OSI inspections and review findings to assist in determining the integrity of the primary efficacy data.”

*Data quality issues*

The first cycle CR letter asked the sponsor to provide information about the BIAL’s QA audit program, and asked for assurance that the safety and efficacy data obtained from Study 301 and 302 are reliable. The Agency suggested an audit, which the sponsor conducted and provided with this submission. Dr. John Lee, from OSI, reviewed the audit findings. Dr. Lee notes that the sponsor's audit of Study 301, 302 and 304 focused on five major GCP categories: (1) informed consent, (2) subject eligibility, (3) subject randomization, (4) Adverse Events (AE) 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 the new Study 304, about three-fourths of subject records were reviewed by the sponsor at 88 clinical sites (39 in North America and 49 in the rest of the world), and at two CRO sites.

There were more adverse reactions identified as “non reported” for Study 301 and 302 in the new audit, compared to the original audit. Dr. Lee believes that this reflects the greater rigor with which the audit was conducted. He notes that the number of deficiencies in Study 302 was significantly greater than in Study 301 (n=167 vs. n=91), for reasons unclear. Serious deficiencies were found at two new sites for Study 301 (lack for source data), and these were removed from the re-analyses (see above). Eligibility violations were much less frequent in Study 304 (n=28), possibly because of the heightened sponsor monitoring and/or fewer subjects per site.

Dr. Lee also discusses that a total of fourteen clinical (GCP) inspections have been performed by FDA, including four sites in the first cycle (with two sites identified as having unreliable data or serious GCP violations), and 10 sites in the current cycle. Dr. Lee notes that the deficiencies were well documented in the sponsor's audit, and that adherence to GCP appeared adequate for all sites inspected, and not appreciably different between US and non-US sites. The FDA findings were consistent with the sponsor's audit findings. Dr. Lee did not see any evidence of unblinding or biased data collection.

Dr. Lee concludes that the overall rate of GCP compliance across all clinical studies and sites appears to be sufficient to support this NDA, with greater confidence for Study 304 than for Study 301 and Study 302. Dr. Podruchny notes that the new audit found a low number of new seizures (0.23%) in Study 301 and Study 302, and these were evenly distributed among the treatment groups, with no significant impact on efficacy findings.

Dr. Lee notes, and Dr. Hershkowitz agrees, that non-biased (e.g., careless and random) deficiencies in the conduct of Study 301, 302, and 304 would be expected to decrease the ability to demonstrate efficacy in these studies. I agree.

### *Data presentation issues*

The first cycle CR letter noted a large number of deficiencies and inconsistencies, which undercut the review team's confidence in the reliability of the data. The CR letter stated that FDA was not certain that the sponsor will be able to adequately salvage the data, and stated that additional studies may be required. As discussed above, an additional study (Study 304) was conducted and submitted to the NDA.

I will first address the reliability of data presentation from Study 304. Dr. Podruchny noted a number of issues in that study. Dr. Podruchny describes an atypical amount of additional clarification, information, and data submission (Dr. Podruchny cites five to six information requests related to efficacy). Dr. Podruchny describes that one request was precipitated by a finding by the statistical reviewer of duplicate entries in the efficacy dataset. The sponsor was asked to perform a comparison of the data from seizure diaries to those entered in the datasets for 40 patients she selected, some of whom had duplicate dataset entries. Dr. Podruchny notes that in the sponsor's initial response to this request, at least two patients with duplicate entries were not identified. Among these, Dr. Podruchny identified a patient who used both an event-based entry diary and a daily entry diary. Dr. Podruchny notes that the patient was not identified by the sponsor, including after a specific query about the existence of any patient in Study 304 who had used both types of diaries and made duplicate entries. Of note, this patient was randomized to active drug, so that the duplication did not favor eslicarbazepine. Dr. Podruchny also noted a page number for a diary that was out of sequence or misnumbered. The sponsor noted that this was an error and that the subject had two diaries with the same entries, but that the duplicated seizures were counted accurately in the maintenance period.

Overall, I agree with Dr. Ling and Dr. Hershkowitz that adequate evidence of efficacy has been provided. The efficacy results from Study 301 and 302 remain essentially unchanged after a thorough audit from the sponsor, and FDA inspections. Study 304, which had a better oversight than the earlier studies, and was also thoroughly audited, 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. There is no evidence that these errors caused an overestimation of the drug effect. If anything, and as noted by Ling, Dr. Lee, and Dr. Hershkowitz, the opposite is true.

## **6. Safety**

Dr. Mary Doi describes multiple deficiencies in the accuracy, reliability, and presentation of the safety data. She notes that in addition to laboratory data missing from the datasets, there were many discrepancies, programming errors, coding omissions, key information missing from the narratives, and narratives of subjects with adverse events of special interest missing. Dr. Doi describes a total of 23 safety information amendments submitted by the sponsor in response to 14 FDA information requests that included approximately 65 separate questions or

items. Dr Doi considers that the most significant deficiency was the occurrence of both missing and incorrect data in the integrated analysis datasets. Nevertheless, Dr. Doi notes that in response to FDA's information requests, the sponsor submitted a multitude of safety amendments that corrected and/or explained these deficiencies.

Dr. Doi describes a database of 4225 eslicarbazepine-exposed subjects from 53 completed trials conducted in Phase 1 volunteers (n=847), patients with partial onset seizures (n=1554), and patients with non-epilepsy indications (n=1832). Dr. Doi identified several safety issues, described below, but she does not consider that any of these precludes approval. Her review focused on the three epilepsy studies described above (Study 301, 302 and 303).

### ***Suicidality***

Dr. Doi identified 8 patients on eslicarbazepine with suicidality, and 2 completed suicides. However, a causal role of eslicarbazepine could not be established. Dr. Doi also notes that the incidence of suicidal thoughts or behavior in eslicarbazepine-treated patients was similar or lower than that estimated from the meta-analysis performed for all antiepileptics drugs. The review team recommends that the standard warning about suicidal behavior and ideation with antiepileptic drugs should be included in eslicarbazepine labeling. I agree.

### ***Skin and Immune Disorders***

Dr. Doi notes that Stevens-Johnson syndrome (SJS) was reported in one patient in clinical trials. There were also two potential cases in the post-marketing database. Dr. Doi discusses that the pre-marketing case of SJS does not meet all of the criteria for probable SJS, but that because of the close temporal relationship with treatment initiation and positive dechallenge, the causal role of eslicarbazepine cannot be ruled out. Dr. Doi also notes an increased incidence of rash (1.9% on drug vs. 0.9% on placebo) and discontinuations due to rash (0.7% on drug vs. 0% on placebo) in epilepsy studies with eslicarbazepine. Dr. Doi notes that severe cutaneous adverse reactions are included in the prescribing information for carbamazepine and oxcarbazepine products, and recommends that similar information be included in the Warnings and Precautions section for eslicarbazepine. I agree.

### ***Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)***

Dr. Doi identified several cases of DRESS in the clinical trials database, and recommends including information about DRESS in the Warnings and Precautions section. I agree.

### ***Anaphylactic reactions and Angioedema***

Dr. Doi notes that eslicarbazepine use is associated with hypersensitivity reactions, such as localized angioedema of eyelids, face, or tongue. Some of these events were serious and led to treatment discontinuation. She notes that although there was no case of anaphylactic reaction in clinical trials, there were reports of possible pharyngospasm and anaphylaxis in the postmarketing database. Dr. Doi recommends a description of hypersensitivity reactions in the Warnings and Precautions section of eslicarbazepine. I agree.

### ***Hyponatremia***

Eslicarbazepine can cause hyponatremia. Serious hyponatremia with related symptoms was observed in clinical trials. The review team recommends including that information in the Warnings and Precautions section. I agree.

### ***Liver toxicity***

Dr. Doi noted a slightly higher incidence of ALT/AST elevations greater than 3 times the upper limit of normal (ULN) in eslicarbazepine-treated patients than in placebo subjects, but identified very few patients with higher grade elevations (i.e., 5x-, 10x-, or 20 xULN). Dr. Doi observes that the sponsor did not report any cases of severe drug-induced liver toxicity (DILI) in the pre-, and post-marketing database. However, Dr. Doi identified two patients who met Hy's law criteria, and in which drug causality cannot be ruled out. Dr. Doi calculates that the number of possible Hy's Law cases equals to 4.7 per 10,000 subjects (or 1.0 per 1,000 subject/years). She estimates the theoretical risk of severe DILI at 10% of this rate, i.e., 0.47 per 10,000 patients (1.0 per 10,000 patient-years). Dr. Doi also observes that there has been no reported post-marketing case of severe DILI, with an estimated exposure of 12,279 patient-years. Dr. Doi recommends that information regarding DILI be included in the Warnings or Precautions section of labeling of eslicarbazepine. She also recommends that in addition to reporting of any case of severe DILI in an expedited manner, the sponsor should be required to perform annual analyses of DILI.

Dr. Senior, FDA DILI expert, essentially agrees with Dr. Doi. He observes that both carbamazepine and oxcarbazepine have been reported to cause rare but serious liver injury, including liver failure and death, and that no evidence has been provided that this cannot occur with eslicarbazepine. Dr. Senior believes that serious liver injury will very likely be very rare, and be preceded by early symptoms of liver dysfunction. I agree with Dr. Doi's and Dr. Senior's assessment and recommendations.

### ***CNS adverse events***

Dr. Doi identified clear dose-related increases in the incidence of several CNS adverse reactions, i.e., dizziness and gait disturbances, somnolence and fatigue, cognitive dysfunction, diplopia and/or vision blurred, and falls. There was also an increase in adverse dropouts because of CNS adverse reactions in eslicarbazepine-treated patients (3.6% on drug vs. 0.2% on placebo). I agree this information should be presented in the Warnings and Precautions section.

### ***Prolongation of PR interval***

Dr. Doi, Dr. Yasuda, and Dr. Hershkowitz discuss a PR interval prolongation signal emanating from clinical trials and from the thorough QT study. As noted by Dr. Hershkowitz, the differences between drug and placebo were small (and of unclear significance), and there was no signal for cardiac-related adverse reactions with eslicarbazepine. Therefore, a description of PR prolongation in labeling is not justified.

### ***Hypothyroidism***

Dr. Doi identified a possible signal for hypothyroidism, with dose-dependent decreases in T3 and T4 values, and concurrent increases in TSH. She recommends including that information

in the Warnings and Precautions section, with a recommendation for baseline and periodic evaluations of thyroid function. Dr. Hershowitz, however, does not believe there is a clear signal, and suspects the decreased T3 and T4 values may be artifactual. This hypothesis should be tested in a post-marketing requirement. The label will warn prescribers that decreases in T3 and T4 were observed, and that abnormal thyroid function tests should be clinically evaluated.

### **REMS**

The review team does not recommend a REMS. Dr. Yasmin Choudhry, from DRISK, agrees that risk mitigation measures beyond labeling do not appear warranted to ensure the benefits of eslicarbazepine outweigh the risks, and that the risks (described above) can be managed through labeling (with a Medication Guide), and routine pharmacovigilance. I agree.

## **7. Pediatrics**

As discussed by Dr. Hershkowitz, the following PREA requirements should apply to this NDA:

- A waiver for patient efficacy studies 1 month and younger
- A juvenile dog toxicology study to identify and characterize the unexpected serious risk of adverse effects of eslicarbazepine acetate on the immune system of the developing organism
- Deferred pharmacokinetic and tolerability study in pediatric patients aged 1 month to < 24 months with partial-onset seizures
- Deferred randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 12 to <18 years for the adjunctive the treatment of partial onset seizures with a long term safety extension
- Deferred randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive the treatment of partial onset seizures with a long term safety extension
- Deferred randomized, controlled, double-blinded, efficacy and safety study of eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years with a long term safety extension.

## **8. Other Relevant Regulatory Issues**

### ***OSI***

I discussed above the OSI review.

### ***DMEPA***

The originally proposed proprietary name, (b) (4), was found unacceptable by DMEPA. The new proposed name, Aptiom, was found acceptable.

### **CSS**

Dr. Lerner, CSS reviewer, concludes that eslicarbazepine acetate exhibited a low abuse potential in clinical studies, and does not recommended scheduling the drug. Dr. Lerner also discusses quality issues that were also observed by other review disciplines (and discussed above), and considers the data on cases of overdoses, medication errors, poisonings and toxicities provided by the sponsor as “not reliable and of questionable quality”. Dr. Lerner describes discrepancies in the numbers of medical errors and overdoses across submissions, with some cases of medications errors coded as “overdose”.

The sponsor explained that the differences between the number of overdose cases in the ISS and in subsequent submissions are due to differences in cut-off dates, and in categorizations of cases (some were apparently coded as medications errors with overdose as a “special term”). The sponsor’s explanation appears confused, and is another example of poor presentation of data in this NDA. However, Dr. Doi reviewed all cases of overdose, including 61 postmarketing cases of overdose that occurred prior to 10/21/12 (the ISS data cut-off date for postmarketing information) but were newly reported in a 9/5/13 amendment. Dr. Doi notes that most of these adverse reactions were consistent with those already known for eslicarbazepine: hyponatremia, seizure related, ataxia, diplopia, vertigo, vomiting, diarrhoea, fatigue/asthenia, rash pruritic, and suicide attempt. Overall, I believe that there is adequate information to write the overdosage section of labeling.

Dr. Lerner found the assessment of drug dependence inadequate, and recommends as a PMR a human dependency study in healthy volunteers. I agree with that requirement.

### **Other**

There are no other unresolved relevant regulatory issues.

## **9. Decision/Action/Risk Benefit Assessment**

I recommend approval of eslicarbazepine.

The original complete response letter was issued mostly because of inadequate study conduct and documentation, and inadequate presentation of the data.

The OSI review (by Dr. Lee) indicates that, based on the extensive auditing of the studies by the sponsor, and FDA inspections of study sites and review of the audits results, the totality of the findings supports the acceptability of the two pivotal studies reviewed in the first cycle (Study 301 and Study 302), and of the new study (Study 304) submitted in this review cycle. In other words, study conduct and documentation issues have been, according to OSI, adequately addressed.

Unfortunately, this application continued (in this submission) to have severe data presentation issues, which led to a considerable number of information requests from the review team. There is disagreement among the team members as to whether the sponsor’s responses

acceptably addressed the data presentations issues, and whether the application can be approved.

Dr. Podruchny, medical officer who reviewed the efficacy of eslicarbazepine, recommends a complete response action, because of “a lack of confidence in the data and a lack of confidence that the processes in place to conduct and/or oversee the trials in a corrective manner and present accurate data functioned/function effectively as supported by evidence of the need for repeated requests of the sponsor for information and clarification in this third 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”. Dr. Ling, statistical reviewer who also reviewed efficacy data, disagrees, and finds that the data support efficacy. Dr. Ling believes that, based on her review of the datasets and of CRFs, the problems noted by Dr. Podruchny were not common. In addition, Dr. Ling did not find in Study 304 the data quality issues she identified for Study 301 and Study 302 in the first review cycle, which is also an observation made by Dr. Lee.

Dr. Hershkowitz, CDTL for this application, also concludes that adequate evidence of efficacy has been provided. Dr. Hershkowitz (and Dr. Lee) argue that data quality issues tend to increase background noise, which would make it more difficult to show a statistically significant effect. I agree with Dr. Hershkowitz and with Dr. Lee. There is no evidence that the issues identified led to a possible overestimation of clinical benefit. Overall, the treatment effect appears similar to that of other approved antiepilepsy drugs, and was fairly consistent across studies. As discussed by Dr. Hershkowitz, there is not a consistently greater benefit of the 1200 mg dose over the 800 mg dose, although some subgroup analyses suggest so, and Study 304 was only positive for the 1200 mg. Overall, I agree with the description of both doses in labeling, allowing for prescribers to titrate individual patients according to response to treatment and tolerability.

Dr. Mary Doi (who review clinical safety) and Dr. Sally Yasuda (safety team leader) also discuss the data presentation issues that were still present in this application. Dr. Doi and Dr. Yasuda however conclude that the safety amendments submitted by the sponsor corrected and/or explained the deficiencies, and they recommend approval. Dr. Doi and Dr. Yasuda identified a number of safety issues, which can be adequately addressed by labeling, and do not justify a REMS, what Dr. Choudhry, from DRISK, agrees with.

I recommend the following Postmarketing Requirements:

- Pediatric studies, as described in Section 7
- A study based on routine postmarketing safety surveillance, pharmacovigilance and clinical trial reports to characterize clinical and genomic risk factors associated with the development of serious dermatologic reactions in eslicarbazepine-treated patients, including Stevens-Johns on syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms (DRESS).
- A physical dependence trial in healthy volunteers
- A study to assess whether the low T3 and T4 values noted in some patients are artifactual.

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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.**  
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/s/  
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ERIC P BASTINGS  
11/06/2013