Cross-Discipline Team Leader Review

Date	September 8, 2017
From	Teresa Buracchio, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22416 Supplement 9
Applicant	Sunovion
Date of Submission	3/13/2017
PDUFA Goal Date	9/13/2017
Proprietary Name / Non-Proprietary Name	Aptiom (eslicarbazepine acetate)
Dosage form(s) / Strength(s)	Tablet; 200 mg, 400 mg, 600 mg, 800 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures as monotherapy or adjunctive therapy for patients 4 years of age and older
Recommendation on Regulatory Action	Approval

1. Background

Eslicarbazepine acetate (ESL) is a dibenz[b,f]azepine compound, the chemical family which also includes the anticonvulsants carbamazepine and oxcarbazepine. The anticonvulsant activity of these agents is thought to be mediated by blockage of the voltage-gated sodium channel (and perhaps calcium gated channels). ESL exhibits functional and structural similarities to oxcarbazepine. ESL is metabolized to S-licarbazepine (eslicarbazepine), R-licarbazepine and oxcarbazepine. Oxcarbazepine produces the same active metabolites, but in different proportions.

Aptiom was approved for the adjunctive treatment of partial-onset seizures in patients 18 years and older in November 2013. The sponsor subsequently received an approval for monotherapy use of Aptiom in the same indication and population in August 2015.

This supplemental application seeks to expand the current indication for the treatment of partial-onset seizures (POS) to include pediatric patients down to 4 years of age based on pediatric extrapolation. The submission will support both monotherapy and adjunctive use of Aptiom in this population. Additionally, this submission will add PLLR format to the prescribing information (PI). The supplement will also address several PREA post-marketing requirements (PMRs) and will partially address a portion of a Written Request.

The Division of Neurology Products (DNP) issued a General Advice letter on November 12, 2015, indicating that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of POS in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults and on an analysis of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS. Extrapolation based on this analysis applies only to POS in pediatric patients 4 years of age and older, and not to POS in pediatric patients 1 month of age to less than 4 years of age or to other forms of epilepsy. The following is required to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:

- Approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

Additionally, DNP also issued a General Advice letter on September 13, 2016, indicating that it is acceptable to extrapolate monotherapy use of a drug approved as adjunctive use for the treatment of POS. To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. To support extrapolation, the sponsor

must provide pharmacokinetic information adequate to demonstrate such similarity, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

There were numerous regulatory interactions with the sponsor regarding requirements for pediatric studies for Aptiom that are outlined in the clinical review for this submission. A Type B pre-NDA meeting was held on August 18, 2016, to specifically discuss the contents of this submission to support pediatric dosing for POS patients aged 4 to 17 years.

2. Product Quality

The sponsor submitted labeling and chemistry, manufacturing and controls (CMC) information to support the addition of a "professional sample" for the 200 mg strength of APTIOM tablets. The 200 mg tablet is already commercially available and there were no changes to the manufacturing of the tablet strength. The submission essentially provided for new packaging for a professional sample. CMC identified no concerns with the submission and found the plan to be acceptable. Carton and container labeling were reviewed by Division of Medical Errors Prevention and Analysis (DMEPA) and were found to be acceptable.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted or required. The nonclinical and safety review teams provided input on the PLLR conversion of the prescribing information.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by reviewers Dr. M. Bewernitz and Dr. D. Li with Team Leaders Dr. K. Krudys and Dr. A. Men.

The sponsor conducted a population pharmacokinetic (PK) analysis (Report COG008041/2014/ESLIPEDS/A) to determine a dosing regimen that would provide similar ESL exposures in pediatric subjects 4 years of age and older to those that were found to be effective in adult subjects with POS. The analysis was based on 3 population PK models developed by the sponsor:

- adult monotherapy model
- adult adjunctive therapy model
- pediatric adjunctive therapy model.

Both the adult monotherapy and adjunctive therapy population PK models provided in this submission were previously reviewed by OCP as part of the original NDA submission (refer to OCP reviews of NDA 022416 signed on 07/23/2015 for further details).

The pediatric adjunctive therapy PK model utilized pooled data from the following studies: BIA-2093-202 (a Phase 2 PK, efficacy, and tolerability study in POS patients aged 2 to 17 years) and BIA-2093-305 (a Phase 3 efficacy and safety study in POS patients aged 2 to 17 years). It is noted that both studies used oral suspension in patients age 2 to 6 years and tablets in patients aged 7 to 18 years. These formulations have been found to be bioequivalent based on studies in adults and can be expected to provide similar exposures to each other in pediatric patients. Although OCP generally agreed with the pediatric adjunctive therapy PK model, they did not agree with (b) (4)

Please see OCP review for a more detailed description of the PK models.

The sponsor conducted PK simulations in virtual adult and pediatric patients to derive pediatric dosing recommendations. The target doses for adults used to derive pediatric dosing recommendations were 400 mg once daily for initiation and titration and the range of 800 mg to 1200 mg once daily for maintenance doses. Note that although ESL is approved for use in adults for doses up to 1600 mg, the sponsor proposed a maximum dose of 1200 mg for pediatric dosing. Additionally, safety data is only available up to the maximum dose of 1200 mg to support pediatric dosing. Dosing recommendations were based on weight groups.

As described in the OCP review, *"the adult simulations were conducted using the adjunctive PK model (where ESL is adjunctive to other anticonvulsant drugs) with the effect of phenobarbital-like AEDs on CL/F, effect of carbamazepine on clearance, and the effect of phenobarbital-like AEDs on V/F. The pediatric simulations were conducted with all drug interaction terms inactive."*

Based on these simulations, the sponsor proposed the following dosing:

Table 1: Sponsor's proposed pediatric dosing

Body Weight Range	Initial and Maximum Titration Increment Dose (mg/day)	Maintenance Dose (mg/day)
11 to 21 kg	(b) (4)	
22 to 31 kg		
32 to 38 kg		
>38 kg		

OCP identified a concern with the simulations that the relationship between monotherapy exposure and adjunctive therapy exposure appeared to be different between weight groups. This finding would not be expected because the PK of ESL should be similar in adults and heavier pediatric patients. Additionally, effects of drug interactions on ESL PK should be comparable between adults and pediatric patients. Based on this finding, OCP felt that there may (b) (4)

Based on these concerns, OCP decided to conduct independent PK simulations in a monotherapy scenario. Their simulations utilized the adult monotherapy PK model and pediatric adjunctive PK model with inactive drug interaction terms to simulate the $C_{min,ss}$ for adults at the approved doses and for a range of pediatric doses. Please refer to the OCP review for details of the analyses conducted.

Using their own simulations, OCP determined that the sponsor's proposed pediatric maintenance dosing would likely result in lower $C_{min,ss}$ than expected exposures for adult dosing in the therapeutic range of 800 mg to 1200 mg. Therefore, OCP recommended revisions to the pediatric maintenance dosing as described in Table 2 below. The proposed pediatric initiation and titration doses appeared to generally match adult exposures, with the exception of the 22 to 31 kg weight group; however, OCP agreed with the sponsor's more conservative dosing recommendation for initiation and titration due to concerns regarding tolerability.

Based on these simulations, OCP developed the following dosing recommendations:

Table 2: OCP recommended dosing for patients aged 4 to < 17 years

Body Weight Range	Initial and Maximum Titration Increment Dose (mg once daily)	Maintenance Dose (mg once daily)
11 to 21 kg	200	400 to 600
22 to 31 kg	200	500 to 800
32 to 38 kg	300	600 to 900
>38 kg	400	800 to 1200

These proposed doses were conveyed to the sponsor in an information request and the sponsor responded on July 17, 2017, with agreement on the proposed doses. However, during final labeling negotiations, the sponsor requested that the initial dose for the 22 to 31 kg weight range be increased to 300 mg. The sponsor's rationale follows: *"The initial and maximum titration increment dosage of 300 mg is approximately 1/2 the lowest maintenance dosage. This is consistent with dosing in the adult adjunctive program, in which the initiation dose was >= 1/2 the lowest maintenance dose (either 400 or 800 mg initial dose). In the adult program, there were no subjects initiated with doses < 1/2 the lowest maintenance dose."*

OCP agreed to this change. Final dosing recommendations to be included in the dosing section of the PI are described in Table 3 below.

Table 3: Final Agreed dosing for patients aged 4 to < 17 years

Body Weight Range	Initial and Maximum Titration Increment Dose (mg once daily)	Maintenance Dose (mg once daily)
11 to 21 kg	200	400 to 600
22 to 31 kg	300	500 to 800
32 to 38 kg	300	600 to 900
>38 kg	400	800 to 1200

OCP also provided the following assessment regarding dosing for the monotherapy use of Aptiom in patients with POS aged 4 to < 17 years:
"Although there are some drugs that interact with ESL (i.e., carbamazepine, phenytoin and phenobarbital) in the adjunctive setting, none are clinically relevant to the extent that they require specific dose adjustments. Based on these considerations, adults have the same dosing for adjunctive therapy as for monotherapy, and it is thus reasonable to apply the same pediatric dosing to monotherapy as is applied to adjunctive therapy in patients age ≥ 4 years."

OCP Recommendation: OCP recommends approval of this supplement with the recommended dosing (Table 3) for pediatric patients aged 4 to 17 years for both monotherapy use and adjunctive use in the treatment of POS. OCP has recommended labeling changes to update pediatric dosing. They also recommend removing statements that the sponsor proposed regarding (b) (4) as these statements do not appear to be supported by their review of the data. They also recommend changes to the formatting of the label regarding the placement of Clinical Pharmacology information. I agree with the OCP recommendations.

5. Clinical Microbiology

No new data submitted or required.

6. Clinical/Statistical- Efficacy

Evidence for the effectiveness of Aptiom in patients with POS aged 4 to 17 years is based on the prior demonstration of efficacy in adult patients with POS. Modeling and simulation was used to provide dosing recommendations for patients age 4 to 17 years that provide similar exposures to those found to be therapeutic in adult patients. Additionally, evidence for the effectiveness of monotherapy use of Aptiom in POS patients age 4 to 17 years is based on the prior demonstration of efficacy when used as adjunctive therapy for the treatment of POS in adult patients and the expectation of similar exposures with monotherapy use of Aptiom to adjunctive use of Aptiom. Refer to Section 4 for a more detailed discussion of these analyses.

As noted in the review by OCP and the clinical review by Dr. Natalie Getzoff that the sponsor previously conducted a randomized, double-blind, placebo-controlled study trial (Study 305) of Aptiom in patients with POS age 4 to 17 years that failed to demonstrate efficacy. The results from this study were previously submitted to the Agency, prior to the issuance of the pediatric extrapolation General Advice letter, and were included in the analysis by OCP that served as the basis for the DNP pediatric extrapolation policy. A careful review of the study by OCP identified a number of factors that may have contributed to the lack of demonstration of efficacy of Aptiom in pediatric patients with partial onset seizures. These factors included:

- lower exposures in younger pediatric patients that may have been subtherapeutic;
- a higher than expected placebo response (especially in the younger patients);
- an imbalance in the baseline seizure frequency between the treatment and placebo groups; and
- differences in baseline concomitant AEDs between the treatment and placebo groups.

Importantly, ESL shares the same active moiety with oxcarbazepine (Trileptal) which has demonstrated effectiveness in the pediatric population.

As noted above, these issues were previously considered and we concluded that Study 305 should be considered a failed study due to study design and execution features. The study results do not impact the ability to extrapolate efficacy from adult patients with POS to pediatric patients with POS age 4 to 17 years.

7. Safety

The safety data in this submission were reviewed by Dr. Natalie Getzoff, DNP clinical reviewer.

As described in Dr. Getzoff's review, the primary sources of safety data were the following:

- Study BIA-2093-305 (Study 305): completed Phase 3 randomized, placebo-controlled, parallel-group, ESL adjunctive therapy (10-30 mg/kg/day, maximum 1200 mg QD) study in patients 2-18 years of age with partial-onset seizures not well controlled by 1 or 2 current AEDs. The primary objective was to assess efficacy of ESL in treating partial seizures in patients 2-18 years of age. The study also included an open-label extension (OLE) phase.
- Study BIA-2093-208 (Study 208): completed Phase 2 randomized, placebo-controlled, parallel-group, ESL adjunctive therapy (10-30 mg/kg/day, maximum 1200 mg QD) study in patients 4-16 years of age with partial-onset seizures not well controlled by 1 or 2 current AEDs. The primary objective was to assess cognitive effects of ESL in pediatric patients. The study also included an OLE phase.
- Study BIA-2093-202 (Study 202): completed Phase 2 open-label PK and safety study of ESL adjunctive therapy (10-30 mg/kg/day, maximum 1800 mg QD) study in patients 4-16 years of age with partial-onset seizures not well controlled by 1 or 2 current AEDs.
- A limited amount of safety data in adolescent patients who were enrolled in adult studies.

There were 485 pediatric patients age 2 to 17 years exposed to ESL. Of these, 421 patients were age 4 to 17 years at the time of enrollment and contributed safety data to support pediatric extrapolation in this age group. Dr. Getzoff conducted her primary safety analysis on pooled data from 362 patients from the double-blind, controlled period of studies 305 and 208. She also analyzed one-year open-label safety data pulled from 337 subjects from Study 202 and the OLE phases of studies 305 and 208. A combined dataset of controlled and uncontrolled data from studies 202, 208, and 305 included 393 patients.

Based on modal daily dose, a total of 241 patients had > 1 year exposure at or above the recommended efficacious doses (by weight categories), and 279 had > 6 month exposure at or above the recommended efficacious doses.

Overall, the safety profile of Aptiom in POS patients age 4 to 17 years was found to be similar to the safety profile in adults and no new safety signals were identified.

7.1. Deaths

There were five deaths reported in the pooled safety population. Of these, four of the patients were receiving ESL.

- A 6 year-old girl who developed "cluster seizures" died on study day 55. The patient was found to have brain herniation, brain edemab and bronchopneumonia.
- A 9 year-old boy who developed a severe infection and associated disseminated intravascular coagulation on study day 1445 died on study day 1449.
- A 4 year-old girl who was hospitalized with bronchopneumonia on study day 824 died on study day 826.
- A 19 year-old woman was found dead with a facial injury on study day 418. Death was presumed due to sudden unexpected death in epilepsy (SUDEP).

Additionally, there was a death in an adult patient reported during the safety review period. A 23 year-old woman was found dead in her bathtub on day 973 of treatment with ESL. The cause of death was ruled as drowning, but seizure or SUDEP could not be ruled out.

None of the deaths were assessed by the investigators, sponsor, or Dr. Getzoff as causally related to ESL.

7.2. Nonfatal Serious Adverse Events

In the controlled safety population, the overall incidence of treatment-emergent SAEs (TESAEs) was higher in in the ESL group (9.9%) than in the placebo group (5.0%). The most-commonly reported TESAEs in ESL patients were seizure-related: partial seizures (ESL 2.5%; PBO 1.9%), status epilepticus (ESL 2.0%; PBO 0%), and convulsion (ESL 1.5%; PBO 0.6%). The only other TESAE that occurred in > 1 patient treated with ESL was bronchopneumonia which reported in Section 7.1 Deaths above. TESAEs that occurred in the open-label safety data were similar to those reported in the controlled safety population. The

incidence and character of TESAEs did not appear to be substantially different from what has been previously reported in the adult clinical trials. No new safety signals were identified.

7.3. Dropouts and Discontinuations

Dr. Getzoff notes that discontinuations in the controlled study population due to TEAEs were low overall. A total of 11 (5.4%) ESL patients and 4 (2.5%) placebo patients discontinued participation in the blinded phase due to a TEAE and only two discontinuations due to TEAEs occurred in more than one patient (2 patients with allergic dermatitis and 4 patients with partial seizures). In the open-label uncontrolled study pool, the overall incidence of discontinuations due to TEAEs was 4.2% and the most commonly-reported TEAE was partial seizures (1.5%). The rates of discontinuations due to TEAEs are lower than those reported in adult clinical trials (15.3%). No new safety signals were identified.

7.4. Common Adverse Events

As noted in Dr. Getzoff's review, a total of 137 of 202 patients in the ESL group (67.8%) and 105/160 patients (65.6%) in the placebo group in the double-blind, controlled study population experienced any TEAE. The most common TEAEs overall in this population were headache (13.9% and 11.3%), somnolence (9.4% and 5.0%), vomiting (7.9% and 5.0%), nasopharyngitis (7.4% and 10.0%), pyrexia (7.4% and 8.8%), and partial seizures (7.4% and 8.8%) in ESL and placebo patients respectively. The incidence and types of TEAEs were similar to those reported in adult clinical trials.

In the one-year open-label data, the overall incidence of TEAEs was 64.1%. The most-commonly reported TEAEs were nasopharyngitis (10.1%), partial seizures (10.1%), vomiting (9.5%), pyrexia (8.6%), headache (8.0%), and somnolence (6.8%). The incidence and types of TEAEs were similar to those reported in the controlled dataset.

The following table, copied from Dr. Getzoff's review, shows the most common TEAEs occurring across the different pooled safety datasets:

Table 4: TEAEs Reported by ≥5% of Patients in Any Study Pool (4 to 17 year olds)

Study Pool	Double-blind Controlled[a]		One-year Open-label Uncontrolled	Post One-year Open-Label Uncontrolled	Combined Controlled and Uncontrolled[b]
MedDRA version 13.1 System Organ Class / Preferred Term	Total PBO N = 160 n (%)	Total ESL N = 202 n (%)	Total ESL N = 337 n (%)	Total ESL N = 177 n (%)	Total ESL N = 393 n (%)
Subjects with any TEAE	**105 (65.6)**	**137 (67.8)**	**216 (64.1)**	**93 (52.5)**	**302 (76.8)**
Eye disorders	**3 (1.9)**	**19 (9.4)**	**23 (6.8)**	**3 (1.7)**	**42 (10.7)**
Diplopia	2 (1.3)	13 (6.4)	15 (4.5)	2 (1.1)	28 (7.1)
Gastrointestinal Disorders	**24 (15.0)**	**38 (18.8)**	**52 (15.4)**	**27 (15.3)**	**97 (24.7)**
Vomiting	8 (5.0)	16 (7.9)	32 (9.5)	12 (6.8)	57 (14.5)
Diarrhoea	4 (2.5)	3 (1.5)	8 (2.4)	10 (5.6)	20 (5.1)
Nausea	3 (1.9)	10 (5.0)	9 (2.7)	1 (0.6)	20 (5.1)
General Disorders and Administration Site Conditions	**22 (13.8)**	**32 (15.8)**	**54 (16.0)**	**20 (11.3)**	**86 (21.9)**
Pyrexia	14 (8.8)	15 (7.4)	29 (8.6)	16 (9.0)	51 (13.0)
Infections and Infestations	**59 (36.9)**	**67 (33.2)**	**137 (40.7)**	**57 (32.2)**	**189 (48.1)**
Nasopharyngitis	16 (10.0)	15 (7.4)	34 (10.1)	15 (8.5)	48 (12.2)
Pharyngitis	10 (6.3)	9 (4.5)	14 (4.2)	9 (5.1)	28 (7.1)
Bronchitis	8 (5.0)	6 (3.0)	14 (4.2)	10 (5.6)	27 (6.9)
Respiratory tract infection	8 (5.0)	11 (5.4)	17 (5.0)	4 (2.3)	24 (6.1)
Rhinitis	8 (5.0)	4 (2.0)	12 (3.6)	11 (6.2)	24 (6.1)
Upper respiratory tract infection	4 (2.5)	5 (2.5)	7 (2.1)	10 (5.6)	23 (5.9)
Viral infection	4 (2.5)	5 (2.5)	12 (3.6)	7 (4.0)	23 (5.9)
Nervous System Disorders	**46 (28.8)**	**73 (36.1)**	**97 (28.8)**	**35 (19.8)**	**169 (43.0)**
Headache	18 (11.3)	28 (13.9)	27 (8.0)	14 (7.9)	57 (14.5)
Partial seizures	14 (8.8)	15 (7.4)	34 (10.1)	19 (10.7)	54 (13.7)
Somnolence	8 (5.0)	19 (9.4)	23 (6.8)	2 (1.1)	49 (12.5)
Dizziness	4 (2.5)	9 (4.5)	10 (3.0)	2 (1.1)	21 (5.3)

[a] Study BIA-2093-305 IMP recall subjects were not included.

[b] TEAEs that occurred since the first dose of ESL in Studies BIA-2093-202, BIA-2093-208, and BIA-2093-305 were included in the analysis. For Study BIA-2093-305 IMP recall subjects, TEAEs that occurred in Part 1 of the study were excluded from the analysis.

Source: ISS, Table 55, verified with JMP

Overall, no new safety signals were identified.

7.5. Adverse Events of Interest

The following adverse events of interest were reviewed by Dr. Getzoff:

Allergic reaction, including rash and hypersensitivity

The sponsor provided a focused analysis of potential allergic reactions in the submission. In the controlled study dataset, the incidence of immune-mediated/allergic reactions was greater in the ESL group than placebo (10.9% and 6.9%, respectively). The most-commonly reported allergic reaction MSEs were allergic dermatitis (3.0% of ESL patients, 0% PBO patients) and rash (1.0% ESL patients, 1.3% of PBO patients). Additionally, a case of drug rash with

eosinophilia and systemic symptoms (DRESS) in a pediatric patient had previously reviewed in the original NDA submission. The Aptiom label already contains warnings for "serious dermatologic reactions" and "DRESS/Multiorgan Hypersensitivity reactions" and "rash" is listed in Section 5. No new safety signals for allergic or skin reactions were identified in this review.

Suicidality
There were no reports of suicidality in the study datasets. There were two reports of suicidal ideation in pediatric patients in the postmarketing reports. Suicidality is a class warning for antiepileptic drugs and is described in the Aptiom label. No new safety signals were identified.

Homicidal Ideation/Behavior
There were no reports of homicidal ideation or behavior in this submission.

Hepatic Events
The Aptiom label contains a warning for drug induced liver injury (DILI). The overall incidence of hepatic events based on TEAEs or laboratory data was 8.5% of ESL patients. There were eight patients treated with ESL who developed liver enzyme elevations (ALT and AST > 3X ULN) during the controlled study and open-label periods. No patients met Hy's law criteria and no patients were discontinued from ESL. The events appear to be consistent with already labeled liver events and no new safety signal was identified.

Hyponatremia
There were no events of hyponatremia during the controlled studies; however, there was one TEAE of hyponatremia and inappropriate antidiuretic hormone secretion (SIADH) and two reports of sodium values < 125 mEq/L in the open-label periods. Hyponatremia is already listed as a warning in the Aptiom label. Additional cases of SIADH were recently identified in a postmarket 915 review (refer to Section 7.8 for more details); therefore, SIADH will be added to the hyponatremia warning.

Hypothyroidism
"Abnormal thyroid function tests" are listed as a warning in the Aptiom label. A signal of abnormal thyroid function tests (TFT) was identified in the adult clinical trials; however, no cases of clinical hypothyroidism were identified. In the controlled study pool, TEAEs of "hypothyroidism" were in 2 (1.0%) patients taking ESL and 1 (0.6%) patient taking placebo.

Dr. Getzoff provides the following assessment of these cases: "*The incidence of hypothyroidism in the pediatric studies was similar in the ESL and placebo groups (1.0% and 0.6%, respectively). The overall incidence in the open label extension period was also low (1.6%). No patients stopped ESL during the study, so no positive or negative dechallenges were reported. All of these patients had confounding factors: all were on at least one concomitant AED, one patient developed the TFT changes while on placebo, and 2 patients had elevated TSH levels at baseline, prior to starting ESL. Identifying causal relationship to ESL is difficult in all cases.*"

Dr. Getzoff also reviewed changes in thyroid function tests. It was a notable finding in the controlled study dataset that free T4 shifted from normal at baseline to out-of-range low for the lowest on-treatment value in 40.3% of ESL patients and 7.1% of PBO patients. However, the mean change was small (-0.206 ng/dL for ESL patients; -0.054 for PBO patients). Additionally, these changes were not associated with other changes in thyroid function tests that would suggest hypothyroidism. The findings appear to be consistent with events described in the Aptiom label. No new safety signal was identified.

Hematologic Events
Dr. Getzoff notes the following in her review: *"For the double-blind controlled study pool, the overall incidence of treatment-emergent cytopenia MSEs was 2.0% of ESL patients (4/202) and 0% of PBO patients, and consisted of neutropenia in 3 ESL patients (1.5%) and anemia in 1 ESL patient (0.5%). In the uncontrolled safety pool (4-17 years), 2 more patients (0.5%) experienced pancytopenia and 1 (0.25%) experienced anemia."* ESL was not discontinued in any of these patients. It is difficult to assess causality because patients were taking numerous concomitant medications. However, a similar hematologic signal was identified in the recent postmarket 915 safety review (refer to Section 7.8 for more details). It is also notable that carbamazepine and oxcarbazepine, which have a similar chemical structure, have warnings in their labels for hematologic events. Based on the 915 review, it was decided to include "hematologic events" as a warning in the Aptiom label. The events described in this review appear to be consistent with the signal identified in the 915 review.

AV Block
There were no reports of TEAEs of 2nd or 3rd degree AV block in the safety population. AV block was assessed in the postmarket 915 review (refer to Section 7.8 for more details).

Seizure exacerbation
As seizures are common in this patient population and can be aggravated by many things, it can be very difficult to determine if an antiepileptic drug exacerbates the underlying seizure disorder. Double-blind, controlled data is most useful in this assessment. As noted in Dr. Getzoff's review, the overall incidence of seizures reported as TEAEs was 8.9% in the ESL group and 6.3% in the placebo group in the pooled controlled dataset. The incidence of seizure was noted to be much greater in Study 305 (ESL: 14.3%, placebo: 7.5%) than in Study 208 (ESL: 1.2%, PBO: 2.5%). However, the overall number of events is low and does not appear to indicate a new safety signal. A significant difference in seizure rates compared to placebo was not previously found in the adult clinical trials. It is also noted that one death due to seizures was previously described in Section 7.1 and was not felt to be causally related to Aptiom.

7.6. Laboratory Findings/Vitals/ECG

See discussion of hyponatremia and hypothyroidism in Section 7.5. No other clinically meaningful changes in laboratory assessments, vital signs, weight, or ECGs were identified by Dr. Getzoff.

7.7. Safety by Age Group

Dr. Getzoff did not identify any differences in the incidence or quality of TEAEs across weight bins, which served as a proxy for age groups in this submission.

7.8. Postmarket Experience

The sponsor submitted an analysis of reports of pediatric postmarketing safety reports from the period of September 2014 to July 2016 which was reviewed by Dr. Getzoff. The pediatric postmarketing reports are consistent with adverse reactions described in Aptiom's label. No new safety signals were identified.

The postmarket safety experience 18 months after approval and after use of Aptiom by at least 10,000 patients was summarized in an FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary Analysis ("915 review"). Please refer to the review by Dr. Getzoff completed on May 30, 2017, for details of the safety assessments. The 915 review identified the following new safety signals:

- Pancreatitis- Three cases of pancreatitis were identified; however, they were all confounded by concomitant medications. Because of the small number of inconclusive cases, it was recommended to continue postmarket monitoring.
- Hematologic events- Six cases reporting hematologic events were identified that provided reasonable evidence of a causal association with eslicarbazepine, two of which were associated with possible DRESS. It is also noted that oxcarbazepine, which is structurally similar to ESL, has a labeled warning for "hematologic events". It was determined that "hematologic events should be added to the Warnings and Precautions section of the label.
- SIADH- Four cases reporting SIADH that provided reasonable evidence of a causal association with eslicarbazepine were identified in the 915 review. Oxcarbazepine and carbamazepine both include wording regarding SIADH under the Warnings and Precautions for hyponatremia. Hyponatremia is already labeled in Aptiom in the Warnings and Precautions section. It was determined that SIADH should be adding to label under existing Warning for hyponatremia.
- AV block- Three cases of AV block were identified that had unclear causal association to ESL. It was recommended to continue postmarket monitoring.

8. Advisory Committee Meeting

None required.

9. Pediatrics

The submission was discussed with the Pediatric Review Committee. The following PREA PMRs will be fulfilled with the approval of this submission:

2099-3 A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 12 years to <18 years for the adjunctive the treatment of partial onset seizures. The primary efficacy endpoint must examine seizure frequency based upon diary data. Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed.

2099-4 Open-label long term extension study for PMR 2099-#3 (A prospective, randomized, controlled, double- blind, efficacy and safety study of eslicarbazepine acetate in children ages 12 years to <18 years for the adjunctive the treatment of partial onset seizures). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed.

2099-5 A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures. The primary efficacy endpoint during the controlled phase must examine seizure frequency based upon diary data. Safety must be evaluated during the controlled phase. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed.

2099-6 Open-label long term extension study for PMR 2099-5 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed.

The following PMRs for monotherapy will be released as they are no longer necessary because of the Division's monotherapy extrapolation policy for POS:

2951-1 Establish the efficacy and safety of APTIOM when used as monotherapy in the treatment of partial-onset seizures in patients 1 month to <18 years of age. This PMR may be fulfilled by a pharmacokinetic/pharmacodynamic analysis of data collected as part of studies of APTIOM as adjunctive treatment of partial-onset seizures in adults and pediatric patients, and as monotherapy treatment in adults. However, if the data from adjunctive treatment studies are insufficient to support the efficacy and safety of APTIOM as monotherapy for partial-onset seizures in any or all pediatric age subsets, additional clinical studies may be required.

2951-2 An open-label, long-term safety study to evaluate the long-term safety of APTIOM when used as monotherapy for partial-onset seizures in patients 1 month to <18 years of age.

Additionally, the submission also partially addresses a portion of the Written Request; however, review for fulfillment of the Written Request will be deferred until all requested studies are completed.

10. Labeling

Please see final label and discussions in the above review.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval.
- Recommendation for Postmarketing Risk Evaluation and Management Strategies: None required.
- Recommendation for other Postmarketing Requirements and Commitments: None.

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/s/

TERESA J BURACCHIO
09/13/2017

WILLIAM H Dunn
09/13/2017