DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022416

NDA APPROVAL

Sunovion Inc.
Attention: Karen Joyce
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) dated March 29, 2009, received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aptiom (eslicarbazepine acetate) Tablets, 200mg, 400 mg, 600 mg, and 800 mg.

We acknowledge receipt of your correspondence and amendments dated:

May 11, 2010	June 18, 2010	August 27, 2010	October 15, 2010	March 18, 2011
March 29, 2011	April 13, 2011	June 24, 2011	June 29, 2011	July 27, 2011
September 23, 2011	October 5, 2011	October 27, 2011	December 2, 2011	March 9, 2012
June 29, 2012	August 31, 2012	September 4, 2012	September 10, 2012	September 20, 2012
September 27, 2012	September 28, 2012	November 27, 2012	December 12, 2012	December 18, 2012
December 20, 2012	February 11, 2013	February 20, 2013	February 25, 2013	February 28, 2013
March 4, 2013	March 11, 2013	March 12, 2013	March 18, 2013	March 22, 2013
March 27, 2013	March 28, 2013	April 2, 2013	April 5, 2013	April 9, 2013
April 15, 2013	April 18, 2013	April 19, 2013	April 23, 2013	April 24, 2013
May 2, 2013	May 6, 2013	Mary 7, 2013	May 8, 2013	May 9, 2013
May 16, 2013	May 20, 2013	May 29, 2013	June 5, 2013	June 10, 2013
June 11, 2013	June 17, 2013	June 21, 2013	June 24, 2013	June 28, 2013
July 1, 2013	July 3, 2013	July 12, 2013	July 24, 2013	July 26, 2013
August 1, 2013	August 8, 2013	August 9, 2013	August 16, 2013	August 23, 2013
August 30, 2013	September 3, 2013	September 5, 2013	September 6, 2013	September 16, 2013
September 19, 2013	September 26, 2013	September 27, 2013	October 2, 2013	October 4, 2013
October 8, 2013	October 10, 2013	October 11, 2013	October 21, 2013	October 25, 2013
October 28, 2013	October 29, 2013	November 8, 2013		

The February 11, 2013, submission constituted a complete response to our April 30, 2010, action letter.

This new drug application provides for the use of Aptiom (eslicarbazepine acetate) 200mg, 400mg, 600mg, and 800mg tablets for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on October 30, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022416**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for eslicarbazepine was not referred to an FDA advisory committee because the safety profile is similar to that of other drugs approved for this indication.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Based on the available stability data, a 24-month expiration date is assigned to the 200 mg strength tablets and a 48-month expiration date is assigned to all configurations of the other three strengths. Drug product should be stored at 25°C (77°F), with temperature excursions in the range of 15°C to 30°C (59°F to 86°F) permitted.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages less than one month old because necessary studies are impossible or highly impracticable due to difficulties in diagnostic certainty in this age group and a small number of available subjects.

We are deferring submission of your pediatric studies for ages one month to < 18 years old for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

2099-1 A juvenile dog toxicology study under PREA to identify and characterize the unexpected serious risk of adverse effects of eslicarbazepine acetate on the immune system of the developing organism. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population.

Final Protocol Submission:	03/2014
Study Completion:	06/2015
Final Report Submission:	12/2015

2099-2 A pharmacokinetic and tolerability study in pediatric patients ages 1 month to < 24 months with partial-onset seizures. At least two maintenance dose levels of eslicarbazepine acetate must be evaluated to characterize pharmacokinetic parameters following at least one week of administration for each dose level of oral eslicarbazepine acetate following titration. Pharmacokinetic data must be

obtained and analyzed using intensive sampling, sparse sampling, or both approaches. If a sparse sampling approach is used, approximately 3-4 blood samples per patient should be collected to enable adequate characterization of the concentration-time profile. At least 20% of patients must come from the 1-month to 6-month age group, and at least 25% of patients must come from the 6- to 12-month and the 12- to 24-month age groups. Effort must be made to balance the gender distribution within each age cohort, with no less than 35% of patients in each gender.

This human study is not to be initiated until juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

Final Protocol Submission: 12/2016
Study Completion: 08/2020
Final Report Submission: 03/2021

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.

Final Protocol Submission: 06/2014
Study Completion: 03/2018
Final Report Submission: 12/2018

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.

Final Protocol Submission: 06/2014
Study Completion: 10/2018
Final Report Submission: 06/2019

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.

This human study is not to be initiated until the juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

Final Protocol Submission:	01/2017
Study Completion:	08/2022
Final Report Submission:	02/2023

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.

This human study is not to be initiated until the juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

Final Protocol Submission:	01/2017
Study Completion:	03/2023
Final Report Submission:	12/2023

2099-7 A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years. The primary efficacy endpoint must examine seizure frequency based upon Video/EEG 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. At least 75% of children in the study should be ≤ 2 years old.

This pediatric study is not to start until the protocol can be informed by the completion and review of the juvenile toxicity study (as requested under PREA PMR 2099-1) because of a potential safety signal in a previous juvenile toxicity study. In addition, this pediatric study should not initiate or enroll subjects in the age group of 1 to 2 years until the pharmacokinetic study requested under PREA PMR 2099-2 is completed.

Final Protocol Submission: 03/2021
Study Completion: 01/2024
Final Report Submission: 07/2024

2099-8 Long term extension study for PMR 2099-7 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years). 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. At least 75% of children in the study should be ≤ 2 years old.

This pediatric study is not to start until the protocol can be informed by the completion and review of juvenile toxicity study (as requested under PREA PMR 2099-1) because of a potential safety signal in a previous juvenile toxicity study. In addition, this pediatric study should not initiate or enroll subjects in the age group of 1 to 2 years until the pharmacokinetic study requested under PREA PMR 2099-2 is completed.

Final Protocol Submission: 03/2021
Study Completion: 08/2024
Final Report Submission: 05/2025

Please allow for adequate time for Agency review and comment on each of the PREA protocols, and for agreement on the protocols, prior to the final protocol submission dates.

Submit the protocols to your IND 067466, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of abnormal thyroid function tests in patients taking eslicarbazepine that may be an artifact of laboratory

interference or to assess a known serious risk for Stevens-Johnson Syndrome and other serious skin reactions in patients taking eslicarbazepine for which risk factors could potentially be identified.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2099-9 An ex vivo study to determine whether eslicarbazepine interferes with assays for free T3 and T4 as well as total T3, T4, and TSH. Collect blood samples from 30 subjects who have taken a daily dose of at least 1200 mg eslicarbazepine acetate for at least 6 weeks, as well as blood samples from 30 non-eslicarbazepine acetate-exposed age-matched subjects. Subjects must not be taking phenytoin, carbamazepine, or oxcarbazepine (or any other drugs known to displace T4 or T3 from binding proteins). Blood samples collected from eslicarbazepine acetate-exposed subjects will be assayed utilizing the clinical trial methods and the most suitable physical separation methodology (e.g., equilibrium dialysis, ultrafiltration, gel filtration) for comparison for serum free T4 and serum free T3 measurements. Blood samples from non-eslicarbazepine acetate-exposed subjects will be spiked with a range of eslicarbazepine and R-licarbazepine concentrations both above and below the known exposures of patients receiving at least eslicarbazepine acetate 1200 mg and assayed utilizing the clinical trial methods and the most suitable physical separation methodology to determine the effect on serum free T3 and T4, as well as effects on serum total T3, T4, and TSH. Results will be evaluated to determine if there is an artifact in the method.

Technical experts familiar with the artifactual effects of certain drugs (e.g., carbamazepine, phenytoin) on decreasing serum free T4 and free T3 with non-physical separation methodologies (e.g., analog immunoassays) will be consulted to determine the most suitable physical separation method (e.g., equilibrium dialysis, ultrafiltration, gel filtration) and a justification of the physical separation methodology will be submitted with the protocol.

The timetable you submitted on October 31, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	03/2016

2099-10 A study based on routine postmarketing safety surveillance, pharmacovigilance and clinical trial reports will characterize clinical and genomic risk factors associated with the development of serious dermatologic reactions in

eslicarbazepine acetate-treated patients, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms (DRESS). The study must include a control group of eslicarbazepine-tolerant patients and use high-throughput genotyping approaches to determine whether specific genotypes are associated with the development of these serious skin reactions.

The timetable you submitted on October 28, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2014
Interim Report Submission:	06/2015
Interim Report Submission:	06/2016
Interim Report Submission:	06/2017
Interim Report Submission:	06/2018
Interim Report Submission:	06/2019
Interim Report Submission:	06/2020
Interim Report Submission:	06/2021
Interim Report Submission:	06/2022
Interim Report Submission:	06/2023
Interim Report Submission:	06/2024
Study Completion:	12/2024
Final Report Submission:	06/2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of serious risk of the potential for serious withdrawal effects when Aptiom (eslicarbazepine acetate) is discontinued abruptly.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2099-11 A prospective human physical dependence trial in healthy volunteers in which subjects are titrated to 800 mg of eslicarbazepine acetate and maintained at this dose for four weeks. At the end of the treatment, the drug should be abruptly withdrawn. Withdrawal should be conducted in an inpatient setting with immediate access to physicians capable of managing medical emergencies (e.g., status epilepticus, cardiopulmonary arrest). Withdrawal questionnaires should be administered at the pre-treatment visit, within the last two days of treatment, on the first day post-treatment, on the fourth to fifth day post-treatment, on the tenth to eleventh day post-treatment, and on the twentieth to twenty-first day post-treatment. All adverse events occurring during the withdrawal period are to be collected. Plasma levels of eslicarbazepine should be measured and accompany

every administration of withdrawal questionnaires through the fifth day post-treatment.

The timetable you submitted on October 28, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2014
Trial Completion:	05/2015
Final Report Submission:	12/2015

Please allow for adequate time for Agency review and comment on each of the PMR protocols and for agreement on the protocols prior to the final protocol submission dates.

Submit the protocols to your IND 067466, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you provide expedited reporting of the following post-marketing adverse events in eslicarbazepine acetate-treated patients:

1) Serious dermatologic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS
2) Severe anemia, pancytopenia, or agranulocytosis
3) Cases of liver injury that meet Hy's law laboratory criteria
4) Second or third degree atrioventricular (AV) block.

We also request that you provide quarterly reports that include a cumulative analysis of each of these events with comparison to the expected background rates. For guidance on supporting data to include for each Hy's law case report please refer to the Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf), particularly sections A.6. (Evaluating Data for Alternative Causes), C (Case Report Forms), and E.4. (Assessment of Hy's Law Cases in the Clinical Trials Database).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Su-Lin Sun, PharmD, Regulatory Project Manager, at (301) 796-0036 or email su-lin.sun@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling (Package Insert and medication Guide)
Carton and Container Labeling

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

/s/

ELLIS F UNGER
11/08/2013