CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022416Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Retraction

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION 1
DIVISION OF NEUROLOGY PRODUCTS

NDA/BLA #s:	022416
Products:	Eslicarbazepine acetate tablets
APPLICANT:	Sunovion Inc.
FROM:	Russell Katz, M.D.
DATE:	October 1, 2012

The NDA for eslicarbazepine acetate was submitted on March 29, 2009. On November 4, 2009, we issued a REMS notification letter informing the applicant that a REMS for eslicarbazepine acetate was necessary to ensure the benefits of the drug outweighed the risk of suicidality. The REMS was to consist of a Medication Guide and a timetable for submission of assessments of the REMS.

On December 4, 2009, Sunovion submitted a proposed REMS in response to our REMS notification letter.

After consultation between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that a REMS for eslicarbazepine acetate tablets is not necessary to ensure the benefits of the drug outweigh the risk described above because we have determined that maintaining the Medication Guide as part of the approved labeling would be adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the REMS to ensure that the benefits of eslicarbazepine acetate outweigh its risks. If this application is approved, the Medication Guide will be subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

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/s/

SU-LIN SUN
10/04/2012

RUSSELL G KATZ
10/29/2012

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Eslicarbazepine Acetate Risk Management Review

Date:	September 29, 2013
Reviewer(s):	Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK) Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Eslicarbazepine acetate tablets
Therapeutic Class:	Antiepileptic
Proposed Indication(s):	For adjunctive therapy in the treatment of partial-onset seizures in age 18 years and above
Dose(s):	400 mg – 1200 mg daily
Subject:	To evaluate the need for a Risk Evaluation and Mitigation Strategy (REMS)
Application Type/Number:	NDA 22416 Resubmission received February 11, 2013
Applicant/sponsor:	Sunovion Pharmaceuticals Inc.
OSE RCM #:	2012-2041

1 INTRODUCTION

This review documents DRISK's evaluation of the need for a Risk Evaluation and Mitigation Strategy (REMS) for new drug application (NDA) 22416, eslicarbazepine acetate oral tablets for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older.

1.1 BACKGROUND

Eslicarbazepine acetate (ESL) is a voltage-gated sodium channel blocking agent with the proposed indication for adjunctive therapy in the treatment of partial-onset seizures in patients age 18 years and older. The proposed dose is 400 mg to1200 mg once daily.

ESL is a pro-drug of eslicarbazepine, a new molecular entity, and an active metabolite of oxycarbazepine. It is structurally similar to carbamazepine (Tegretal), and oxcarbazepine (Trileptal).

According to the sponsor, approximately 2.2 million people in US have epilepsy at any one time, and 1/3 of persons with epilepsy are not adequately treated with the current antiepileptic drugs; this may largely be due to incomplete response and insufficient adherence to therapy due either to poor tolerability, or complicated dosing regimens[1]. The sponsor states that currently available antiepileptic drugs are associated with adverse reactions (hepatic, hematologic, dermatologic and teratogenic) which limit their use; and most antiepileptics are dosed two or more times per day. The sponsor's rationale for developing ESL is to address the unmet medical need of once daily dosing.
ESL is currently approved in 36 countries.

During the original application cycle, DNP notified Sunovion that a Medication Guide (MG)-only REMS will be required for NDA 22416 to mitigate the risk of suicidal thoughts/behavior associated with ESL consistent with the class of antiepileptics. Sunovion submitted a MG-only REMS on January 8, 2010; however, a CR was issued for the application in April of that same year for deficiencies in the conduct/documentation of studies, and the accuracy, reliability, and presentation of data.

On November 2, 2012, DNP issued an incomplete response letter and notified Sunovion that a REMS was not necessary (a rationale was not provided in the letter); however, during team discussions it became evident that the decision was based on the fact that REMS for the class of antiepileptics was eliminated and that the team believed that the risks can safely be communicated via labeling and a MG outside of a REMS.

[1] Sunovion Pharmaceuticals: Clinical Overview, submission dated August 31, 2012.

2 REGULATORY HISTORY

March 30, 2009: FDA received Sunovion's original NDA 22416 for eslicarbazepine acetate tablets.
November 4, 2009: DNP notified Sunovion that a MG-only REMS will be required.
January 8, 2010: Sunovion submitted a REMS Amendment that included a MG-only REMS.
April 30, 2010: A Complete Response (CR) was issued for deficiencies in the application.
August 31, 2012: Sunovion resubmitted NDA 22416.
November 2, 2012: Incomplete Response letter was issued by FDA; in this letter DNP also notified Sunovion that a REMS for eslicarbazepine will not be required. Sunovion resubmitted NDA 22416 dated February 8, 2013 (received February 11, 2013).
May 8, 2013: The PDUFA goal date was extended (from August 10, 2013 to November 8, 2013) in response to a major amendment that included additional clinical data (received February 11, 2013).

3 MATERIALS REVIEWED

- Sunovion's clinical efficacy/safety documents for NDA 22416 for eslicarbazepine acetate dated March 29, 2009.
- Clinical safety review for NDA 22416 by Mary Doi, M.D., M.S., dated September 9, 2013.
- Safety Team Leader Memorandum for NDA 22416 by Sally Usdin Yasuda dated September 16, 2013.

3.1 OVERVIEW OF CLINICAL PROGRAM

3.1.1 Efficacy & Non-Clinical

Efficacy of ESL as adjunctive therapy in partial-onset seizures was demonstrated[2] in the following Phase 3 studies:

- Study 2093-301
- Study 2093-302
- Study 2093-304

All 3 studies were randomized, placebo-controlled, parallel group, and multicenter in patients with seizures; duration of the studies was 12 weeks and the primary end point was reduction in seizure frequency rates. The dosages evaluated were 800 and 1200 mg.

[2] Statistical review and evaluation of clinical studies NDA 22416 by Xiang Ling, Ph.D., dated September 10, 2013.

This efficacy information is from the clinical safety review by Dr. Doi. The efficacy clinical review is still pending.

3.1.2 Safety

The sponsor's safety data base for ESL included data from 53 completed studies (>4000 subjects exposed) in healthy volunteers, subjects with partial onset seizures, and subjects with non-epilepsy indications of bipolar disorder, neuropathic pain, migraine, and fibromyalgia.

The clinical reviewer's focus of the safety review[3] was the pooled data from the Phase 3 studies in a total of 1021 subjects with epilepsy.

3.1.2.1 Sponsor Reported Safety Findings

The sponsor proposed that the following adverse events be included in the Warnings & Precautions Section of the label:

- Suicidal behavior/ideation
- Hypersensitivity reactions including skin rashes and drug reaction with eosinophilia
- Hyponatremia
- Neurologic events including dizziness, coordination, balance disorders, gait disturbance, somnolence, and sedation
- Withdrawals of antiepileptic drugs.

3.1.2.2 Clinical Reviewer's Safety Findings

The clinical reviewer agrees with the sponsor's findings of safety; however, additional safety issues that resulted in serious and life-threatening outcomes were identified by the clinical reviewer including:

- Drug-induced liver injury: In clinical trials, there was a slightly higher incidence of transaminase elevations of > 3x upper limit of normal (ULN) without bilirubin elevations ESL treated subjects than placebo.

  Three subjects with elevations of transaminases > 3x ULN and bilirubin > 2x ULN, and two cases of Hy's law (> 3x ULN associated with total bilirubin > 2x ULN and alkaline phosphate < 2x ULN) were identified by the clinical reviewer with an estimated risk of 4.7 per 10,000 patients. Of the two Hy's law cases, one subject had a history of chronic pancreatitis and hypertension, and the other subject had a history of hepatic steatosis, diabetes and hypertension. The second subject was not technically considered (by the

[3] Clinical safety review NDA 22416 by Mary Doi, M.D., M.S., dated September 9, 2013

clinical reviewer) a Hy's law case because of confounders (use of paracetamol during the clinical trial and lack of investigation by the investigator of alternative etiologies for liver disease). Neither of these cases resulted in death or transplantation.

The clinical reviewer's calculated risk for hepatic toxicity, based on the estimate from the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation[4], is 2/4225 or 4.7 per 10,000 patients, and the risk of severe drug induced liver injury (DILI) is 10% of that or 0.47 per 10,000 patients which is less than the frequency of severe DILI for most drugs withdrawn (<1 per 10,000) from the market according to the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Additionally, with over 12,000 patient years of exposure worldwide, severe DILI cases were not reported.

The clinical reviewer recommended that drug induced liver injury should be included in the Warnings & Precautions section of ESL label, severe cases of DILI should be reported in an expedited manner, and that in order to mitigate the risk of liver injury, monitoring of liver tests should be performed prior to initiation of the drug and then periodically. Results of a hepatology consult are pending.

- Serious skin reactions: ESL use was associated with increased occurrence of rash compared to placebo; however, the rates were low (ESL 1.9% versus placebo 0.9%). One possible case of Steven Johnson Syndrome was identified which was confounded by lamotrigine use. The clinical reviewer recommended that these risks be included in the Warnings & Precautions of the ESL label; serious skin reactions are also included in the prescribing information for carbamazepine and oxcarbazepine.

- Anaphylactic reactions/angioedema: ESL use was associated with hypersensitivity reactions such as localized angioedema of the face, tongue and eyelid; however, the numbers were small (<0.5%) and these symptoms were seen to begin and resolve quickly. No cases of anaphylactic reactions were noted. The clinical reviewer recommended that these risks be included in the Warnings & Precautions.

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A total of 5 cases of DRESS were identified with ESL use. The clinical reviewer recommended including this risk under the Warnings & Precautions.

- Neurological events: Cognitive dysfunction, visual changes, falls and injuries occurred twice as often in ESL subjects than placebo. A dose response

[4] Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration October 12, 2007

relationship was observed with 800 mg and 1200 mg; particularly, falls without seizures were seen in 45% in the ESL group versus 16% in placebo. The clinical reviewer recommended including this risk under the Warnings & Precautions.

- Suicidality: Eight ESL subjects with suicidality were identified in the safety database; because of prior history of depression in these subjects, it was difficult to establish causality with ESL. Slightly more treatment emergent psychiatric disorders were seen with ESL than with placebo (11% vs 10%). This risk was consistent with the approved antiepileptics and the clinical reviewer recommended including the class labeling language regarding suicidality in the ESL label.

A total of 19 deaths from the clinical development program were reported by the sponsor; a causal relationship to ESL was not determined in most of the death (three were possibly related).

The clinical reviewer recommended that:

- The additional safety issues identified should be included in the Warnings & Precautions of the ESL label. The ESL label is still under review.

- A Medication Guide should contain the suicidality warning (as required by DNP for all antiepileptic medications).

- Postmarketing requirements:

  - Genetic risk factors for developing severe cutaneous adverse reactions, specifically the association with the presence of HLA alleles (e.g., HLA-B*1502, HLA-A*3101).

  - Association between ESL use and acid-base abnormalities.

  - Additionally, the clinical reviewer recommended expedited reporting of any cases of severe DILI along with annual analyses and reports of DILI; and postmarketing surveillance for anemia.

The non-clinical profile of ESL in regards to terratogenicity (cleft palate and vertebral anomalies), and carcinogenicity (hepatocellular carcinoma) is consistent with the other FDA approved antiepileptics[5].

The clinical reviewer did not recommend a REMS.

[5] Pharmacology/Toxicology review NDA 22416 by Christopher D. Toscano dated April 14, 2010.

4 RISK MANAGEMENT PROPOSED BY APPLICANT

Sponsor's proposed risk management plan voluntarily submitted (February 11, 2013) was comprised of (b) (4)

5 DISCUSSION

ESL is an antiepileptic drug (AED) that is structurally similar to the AEDs carbamazepine and oxcarbazepine and is an active metabolite of oxcarbazepine. The proposed indication is for adjunctive therapy in the treatment of partial-onset seizures for patients with epilepsy18 years and older. The clinical efficacy review has not yet been finalized.

The primary safety concerns include drug induced liver injury (DILI), serious skin reactions, anaphylactic reactions/angioedema, DRESS, and suicidality. Regarding the risk for DILI, the clinical reviewer's calculated risk for hepatic toxicity, is 2/4225 or 4.7 per 10,000 patients, and the risk of severe DILI is 0.47 per 10,000 patients which is less than the frequency of severe DILI for most drugs withdrawn (<1 per 10,000) from the market according to the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Additionally, with over 12,000 patient-years of exposure worldwide, severe DILI cases were not reported. The clinical safety reviewer is recommending all of these safety issues be included in the warnings and precautions section of the label (the ESL label is currently under review).

The clinical review team believes that the risks associated with ESL, particularly liver toxicity and serious skin disorders, are consistent with the approved products oxcarbazepine and carbamazepine and do not warrant a REMS. Moreover, these approved anticonvulsants do not have a REMS. Based on what we know at this time DRISK agrees that a REMS does not appear warranted for ESL.

6 CONCLUSION

In conclusion, risk mitigation measures beyond labeling do not appear warranted for ESL to ensure the benefits outweigh the risks. The risks associated with ESL can be managed through labeling that includes a MG and routine pharmacovigilance.

Should DNP raise further concerns regarding safety of ESL and believe that a REMS may be necessary to mitigate the risks, we will re-evaluate our recommendation. DRISK will continue to follow this NDA.

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/s/

YASMIN A CHOUDHRY
09/29/2013

CLAUDIA B MANZO
09/29/2013
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 4, 2010
To:	Russell Katz, M.D., Director **Division of Neurology Products**
Through:	Claudia Karwoski, Pharm D, Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Barbara Fuller, RN, MSN, CWOCN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	Memo to file re: Review of Patient Labeling (Medication Guide), and Risk Evaluation Mitigation Strategy (REMS)
Drug Name(s):	Stedesa (eslicarbazepine acetate) Tablets
Application Type/Number:	NDA 22-416
Applicant/sponsor:	Sepracor Inc.
OSE RCM #:	2009-731

The Division of Neurology (DNP) requested that the Division of Risk Management (DRISK) review the proposed patient labeling and Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA) 22-416 submitted by Sepracor Inc. for Stedesa (eslicarbazepine acetate) Tablets.

DNP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide-only REMS until such time as the review division plans to address labeling. Please send us a new consult at that time. This memo serves to close out the consult request for Stedesa (eslicarbazepine acetate) Tablets.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

BARBARA A FULLER
03/04/2010
DRISK Stedesa MG REMS Deferral Memo

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03/04/2010
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Neurology Products

NDA/BLA #s:	NDA 22416
Products:	Stedesa (eslicarbazepine acetate) 400mg, 600mg and 800mg Tablets
SPONSOR:	Sepracor
FROM:	Russell Katz, M.D.
DATE:	October 21, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Stedesa (eslicarbazepine acetate) to ensure that the benefits of the drug outweigh the increased risks of suicidal thoughts and behavior with the class of antiepileptic drugs (AED), of which Stedesa (eslicarbazepine acetate) is a member. In reaching this determination, we considered the following:

A. Stedesa (eslicarbazepine acetate) is not yet approved, therefore it is not possible to precisely estimate the size of the population likely to use this product; however it is anticipated to be large, based on the use of antiepileptic drugs in general. The prevalence of epilepsy has been estimated at 5-10 persons per 1000.[1] The total number of patients receiving a prescription for any of 11 antiepileptic drugs included in the meta-analysis of the risk for suicidal thoughts and behavior with antiepileptic drugs (described below in Section E) in outpatient retail pharmacies in the United States was over 11 million in 2007.

[1] Harrison's Principles of Internal Medicine, 17th Ed. (2008).

Some antiepileptic drugs, however, are also approved for the treatment of conditions other than epilepsy.

B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy.[1] Seizures may cause significant trauma, drowning, and accidental injury. Many of the deaths in persons with epilepsy are directly related to seizures, accidents and injuries arising from seizures, and the underlying condition resulting in seizures.

C. The efficacy of Stedesa (eslicarbazepine acetate) for the treatment of partial onset seizures was studied in two phase 3 placebo-controlled trials and one supportive phase 2 placebo-controlled trial. The applicant has concluded that the available data support the efficacy of Stedesa (eslicarbazepine acetate) as adjunctive therapy in the treatment of partial-onset seizures adults with epilepsy. These trials are currently under FDA review.

D. If approved, duration of treatment with Stedesa (eslicarbazepine acetate) is expected to be chronic.

E. A known serious risk of AEDs as a therapeutic class is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The increased risk of suicidal thoughts and behavior were demonstrated in a meta-analysis of randomized, placebo-controlled clinical trial data for 11 AEDs. 2 In this meta-analysis, 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use. The background incidence of suicide in patients with epilepsy is estimated as being higher than the incidence of suicide in the general population.

Although the Division has not completed its review, the company proposes the following be included in addition to that of suicidal behavior and ideation in the Warnings section: serious dermatological reactions, hyponatremia, cognitive/neurological impairment, (b) (4) and increased seizures upon cessation of use.

F. Stedesa (eslicarbazepine acetate) is a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Stedesa (eslicarbazepine acetate). FDA has determined that Stedesa (eslicarbazepine acetate) poses a serious and significant

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[2]Statistical review and evaluation: Antiepileptic drugs and suicidality. (Accessed September 24, 2008, at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf.)

public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Stedesa (eslicarbazepine acetate). FDA has determined that Stedesa (eslicarbazepine acetate) is a product for which patient labeling could help prevent serious adverse events and that Stedesa (eslicarbazepine acetate) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Stedesa (eslicarbazepine acetate).

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

DOROTHY J DEMCZAR
10/27/2009

RUSSELL G KATZ
11/06/2009