CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022399Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

NDA/BLA #s:	022399
Products:	Horizant (gabapentin enacarbil) Extended-Release Tablets 600mg
APPLICANT:	GlaxoSmithKline
FROM:	Ellis F. Unger, M.D.
DATE:	April 6, 2011

The purpose of this memorandum is to document the rationale for retracting the requirement for a risk evaluation and mitigation strategy (REMS) for Horizant (gabapentin enacarbil) Extended-Release Tablets as stated in our REMS notification letter dated September 21, 2009. The REMS was required to ensure that the benefits of Horizant (gabapentin enacarbil) Extended-Release Tablets would outweigh the risks of suicidality and potential adverse effects on patients' ability to drive. Our rationale for requiring a REMS at that time was documented in a memorandum also dated September 21, 2009. The REMS was to include the following elements: a Medication Guide and a timetable for submission of assessments of the REMS. The New Drug Application for Horizant (gabapentin enacarbil) Extended-Release Tablets is still pending final action on the April 6, 2011 PDUFA deadline.

The February 2011 Draft Guidance for Industry entitled *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*, states that the FDA may approve a Medication Guide under 21 CFR 208 without requiring the Medication Guide to be a part of a REMS when the Medication Guide is adequate to address the serious and significant public health concern and meets the standard set forth under that regulation.

The Division of Neurology Products (DNP) in the Office of New Drugs (OND), and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) have determined that a REMS for Horizant (gabapentin enacarbil) Extended-Release Tablets is no longer necessary because labeling will be adequate to describe the serious risks described above. The Medication Guide will be part of the approved labeling and be subject to the requirements under 21 CFR 208.

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/s/

SUSAN B DAUGHERTY
04/06/2011

ELLIS F UNGER
04/06/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation 1
Division of Neurology Products

NDA/BLA #s:	22-399
Products:	Gabapentin enacarbil, Extended-Release Tablets (Proprietary name to be determined)
SPONSOR:	GlaxoSmithKline
FROM:	Dr. Russell Katz, M.D.
DATE:	August 27, 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 gabapentin enacarbil to ensure that the benefits of the drug outweigh the risks of suicidality and potential adverse effects on patients' ability to drive. In reaching this determination, we considered the following:

A. The prevalence of Restless Legs Syndrome (RLS) in the United States (U.S.) can be estimated using data from a population-based study that included subjects from the U.S., France, Germany, Spain, Italy, and the United Kingdom. The U.S. was by far the largest contributor to the study database, accounting for 5,964/15,391 completed questionnaires. In this study, the estimate of adults (>18 years old) with moderate to severely distressing symptoms of RLS was reported as 3.1% of respondents living in the U.S.[1]. The U.S. Census Bureau estimates that the number of adults ≥18 years old

[1] Richard P. Allen, PhD; Arthur S. Walters, MD; Jacques Montplaisir, MD, PhD; Wayne Hening, MD, PhD; Andrew Myers, PhD; Timothy J. Bell, PhD; Luigi Ferini-Strambi, MD Restless Legs Syndrome Prevalence and Impact REST General Population Study Arch Intern Med. 2005;165:1286-1292

living in the U.S. is 118,026,789.[2] Thus, approximately 3,658,830 adults potentially need treatment for RLS in the U.S.

B. RLS is a non-life threatening sleep disturbance. It has been associated with a number of co-morbid conditions (anxiety, depression, increased risk for cardiovascular disease, excessive daytime sleepiness), although no clear causal relationship has been established between RLS and these conditions.

C. Gabapentin enacarbil has been demonstrated to be effective in the treatment of moderate to severe symptoms of primary RLS. In the two pivotal clinical trials (XP052 and XP053), gabapentin enacarbil was associated with a 13 point (13.8 at 600 mg/day to 13.1 at 1200 mg/day) improvement in the International Restless Legs Syndrome (IRLS) rating scale, compared to a 9.2% improvement in the placebo-treated group. The improvement in the IRLS rating scale was associated with improved patient-reported CGI (clinical global impression) scale responder rate. 42% of placebo-treated subjects were responders versus 79% (600 mg/a day) and 74% (1200 mg/day) of gabapentin enacarbil-treated subjects.

D. Treatment with gabapentin enacarbil is expected to be chronic.

E. Gabapentin enacarbil is the prodrug of gabapentin (an antiepileptic drug), which is associated with an increased risk for suicidal thoughts and behaviors. As such, it is expected to share this risk. A known serious risk of antiepileptic drugs 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 was demonstrated in a meta-analysis of randomized, parallel-arm, placebo-controlled clinical trial data for 11 AEDs. In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); 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. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use.

   In addition, one case of a completed suicide, one case of a possible suicide, and one suicide attempt were reported to have occurred in subjects receiving gabapentin enacarbil in clinical trials supporting this NDA. There were no similar events reported among subjects who were assigned to receive placebo. There are no available data describing the background risk for suicidality in patients with moderate to severe symptoms of RLS.

   In addition, gabapentin enacarbil is associated with potential adverse effects on patients' ability to drive. Lane position variability studies were conducted by the sponsor to simulate gabapentin enacarbil's effects on driving. The effect produced by

[2] Source: Population Division, U.S. Census Bureau

1200 mg of gabapentin enacarbil given the evening before the driving assessment was similar to the effect of 50 mg of diphenhydramine taken 2 hours prior to evaluation.

Gabapentin enacarbil is also associated with other adverse events including somnolence and potential adverse effects on the developing fetus. It also may cause seizures if stopped suddenly.

F. Gabapentin enacarbil is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for gabapentin enacarbil. FDA has determined that gabapentin enacarbil poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of gabapentin enacarbil. FDA has determined that gabapentin enacarbil is a product for which patient labeling could help prevent serious adverse effects and 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 gabapentin enacarbil.

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-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLINE	SOLZIRA

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/s/

BEVERLY A CONNER
09/15/2009

RUSSELL G KATZ
09/17/2009