CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022399Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022399

NDA APPROVAL

Glaxo Group Limited
d/b/a GlaxoSmithKline
Attention: Debra Lake, M.S.
Manager, U.S. Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Lake:

Please refer to your new drug application (NDA) dated January 8, 2009, received January 9, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Horizant (gabapentin enacarbil) Extended-Release Tablets 600 mg.

We acknowledge receipt of your amendments dated October 6, November 11, and December 21, 2010, and February 15, March 2, 4, and 15, and April 5, and 6, 2011.

The October 6, 2010, submission constituted a complete response to our February 16, 2010, action letter.

This new drug application provides for the use of Horizant (gabapentin enacarbil) for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults.

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

Your application for Horizant was not referred to an FDA advisory committee because the safety profile is acceptable for RLS and the clinical study design is similar to previously approved products in the class.

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, and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for

industry titled "SPL Standard for Content of Labeling Technical Qs and As" 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 container labels that are identical to the carton and immediate container labels submitted on March 15, 2011, 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 titled "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 022399."** Approval of this submission by FDA is not required before the labeling is used.

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

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 12 years because the necessary studies are impossible or highly impracticable. There are too few patients in this population with clinically significant RLS symptoms for enrollment in a study.

We are deferring submission of your pediatric studies for ages 13 to 16 years for this application until additional safety or effectiveness data have been collected. Adult studies evaluating efficacy with a lower strength dose are necessary before pediatric studies are to begin.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act 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 Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1588-1 Conduct a PK/PD study in adolescents ages = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

Final Protocol Submission: 01/2015
Study Completion: 06/2016
Final Report Submission: 06/2017

1588-2 Conduct a double-blind, randomized, placebo-controlled, parallel group efficacy and safety evaluation trial in adolescents = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

Final Protocol Submission: 06/2015
Study Completion: 10/2023
Final Report Submission: 10/2024

1588-3 Conduct a long-term safety study of adolescents ages =13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. The study must provide a descriptive analysis of safety data in pediatric patients during at least 12 months of continuous treatment with gabapentin enacarbil at individualized doses in association with the study described in PMR #1588-2.

Final Protocol Submission: 01/2016
Study Completion: 07/2024
Final Report Submission: 07/2025

1588-4 Conduct a driving study in adolescent patients of legal driving age who have Restless Legs Syndrome, using diphenhydramine as active control.

Final Protocol Submission: 06/2017
Study Completion: 06/2021
Final Report Submission: 06/2022

Submit draft protocols in advance to allow for comments by the Division prior to final protocol submission.

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s).**"

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:

- an unexpected serious risk due to potential inhibition of CYP2C8 and CYP2B6 and resultant drug-drug interactions with concomitant medications
- an unexpected serious risk due to rapid dissolution of Horizant tablets and increased absorption and exposure to Horizant (and gabapentin) if taken with alcohol

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

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

1588-5 An *in vitro* study to evaluate the potential for gabapentin enacarbil and gabapentin to be inhibitors of CYP2C8 and CYP2B6.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2011
Study Completion:	08/2011
Final Report Submission:	10/2011

1588-6 An *in vitro* dissolution study to evaluate alcohol dose dumping using the final dissolution method, and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2011
Study Completion:	04/2011
Final Report Submission:	06/2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient:

- to assess a known serious risk related to adverse effects on patients' ability to drive,
- to identify an unexpected serious risk due to prolongation of the QTc interval in patients taking Horizant, and
- to identify an unexpected risk associated with an increased exposure to gabapentin due to a drug interaction with morphine.

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

1588-7 A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin enacarbil that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2011
Study Completion:	10/2011
Final Report Submission:	02/2012

1588-8 A simulated driving trial in healthy adult subjects treated with an appropriate dose of gabapentin enacarbil determined in PMC 1588-12 that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2014
Study Completion:	05/2015
Final Report Submission:	09/2015

1588-9 An adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate the effect of gabapentin enacarbil on cardiac repolarization in healthy adult subjects.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2011
Trial Completion:	05/2012
Final Report Submission:	11/2012

1588-10 A clinical drug-drug interaction trial to evaluate the pharmacokinetic and the pharmacodynamic interaction between gabapentin enacarbil and morphine.

The timetable you submitted on April 1, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2011
Trial Completion:	12/2011
Final Report Submission:	04/2012

Submit draft protocols in advance to allow for comments by the Division prior to final protocol submission.

Submit the protocols to your IND 073512, 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1588-11 Develop a dosage form that will allow for a 300 mg dose that could be taken once daily in patients with severe renal impairment, including patients on hemodialysis.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2011
Study/Trial Completion:	06/2011
Final Report Submission:	06/2011

1588-12 Conduct a randomized, placebo-controlled, double-blind, parallel-group clinical trial of gabapentin enacarbil at 300 mg/day, 450 mg/day and 600 mg/day in patients with moderate to severe symptoms of RLS.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2012
Trial Completion:	07/2014
Final Report Submission:	02/2015

Submit clinical protocols to your IND 073512 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In our letter dated September 21, 2009, we notified you that a risk evaluation and mitigation strategy (REMS) was required for Horizant (gabapentin enacarbil) to ensure that the benefits of the drug outweigh the risks of suicidality and potential adverse effects on patients' ability to drive. We indicated that your REMS must include a Medication Guide and timetable for submission of assessments of the REMS.

We acknowledge receipt of your proposed REMS as described in your October 9, 2009, January 28, 2010, and October 6, 2010 submissions. The proposed REMS, as amended, contains a Medication Guide and a timetable for submission of assessments of the REMS.

We have determined that is not necessary for the Medication Guide to be part of a REMS to ensure that the benefits of Horizant (gabapentin enacarbil) outweigh its risks. We believe that the Medication Guide is necessary for patients' safe and effective use of Horizant (gabapentin enacarbil), and it will be part of the approved labeling and subject to the requirements under 21 CFR 208.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing,

Advertising, and Communications (DDMAC), see
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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 Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
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
04/06/2011