DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-008

NDA APPROVAL

SmithKline Beecham d/b/a/GlaxoSmithKline
Attention: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your new drug application (NDA) dated February 9, 2007, received February 9, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Requip XL (ropinirole) Extended-Release Tablets 2, 3, 4, and 8 mg.

We acknowledge receipt of your submissions dated December 17, 2007, January 30, February 1, 11, and 13, April 11, and June 10 and 11, 2008.

The December 17, 2007, submission constituted a complete response to our December 7, 2007 action letter.

This new drug application provides for the use of Requip XL (ropinirole) Extended-Release Tablets for the treatment of signs and symptoms of idiopathic Parkinson's disease.

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.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert) Upon receipt, we will transmit that version to

the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-008."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels 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 (October 2005).* 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 22-008**." 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 this application because necessary studies are impossible or highly impracticable. There are too few pediatric patients with idiopathic Parkinson's disease to study.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

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 a serious risk, that is, the potential for patients to experience varying serious adverse events depending on the dose of ropinirole administered . We believe that there is a potential for a signal of a serious risk correlated to dose level.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess this signal of a serious risk.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess this signal of a serious risk dependent on dose.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

1. Conduct a fixed-dose, placebo-controlled, double-blinded study that examines multiple doses in early Parkinson's disease. The trial should identify a range of doses inclusive of the lowest effective dose and the lowest maximally effective therapeutic dose.

Protocol Submission:	by October 31, 2008
Study Start:	by July 31, 2009
Final Report Submission:	by July 31, 2012

2. Conduct a fixed-dose, placebo-controlled, double-blinded study that examines multiple doses in late Parkinson's disease. The trial should identify a range of doses inclusive of the lowest effective dose and the lowest maximally effective therapeutic dose.

Protocol Submission:	by October 31, 2008
Study Start:	by July 31, 2009
Final Report Submission:	by July 31, 2012

Submit the clinical protocols to your IND 60,503 for this product with a cross reference to this NDA 22-008. Submit all study final reports to this NDA 22-008. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing clinical trials as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of these postmarketing clinical trials pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with Requip XL (ropinirole extended-release tablets).

POSTMARKETING COMMITMENT

We remind you of your postmarketing study commitment in your submission dated December 17, 2007. This commitment is listed below.

3. Evaluate whether ropinirole is a P-gp substrate and/or inducer for major CYP enzymes (e.g., CYP3A4) and, if so, any drug-drug interaction potential through either mechanism. This can be accomplished through a comprehensive literature review or by conducting an in vitro study.

Protocol Submission:	by August 2008
Study Start:	by September 2008
Final Report Submission:	by July 2009

Submit clinical protocols to your IND 60,503 for this product with cross reference to NDA 22-008. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA 22-008. 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, number of patients entered into each study.

Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Postmarketing Commitment Protocol**
- **Postmarketing Commitment Final Report**
- **Postmarketing Correspondence**
- **Annual Status Report of Postmarketing Commitments**

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(s) 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(s), 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 www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: labeling

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

/s/

Russell Katz

6/13/2008 02:20:10 PM