DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020505/S-042
NDA 020844/S-036

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C
Attention: Christine Grundy, PharmD
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560

Dear Dr. Grundy:

Please refer to your Supplemental New Drug Applications (sNDA) dated June 16, 2010, received June 17, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Topamax® (topiramate) Tablets and Topamax® (topiramate) Sprinkle Capsules.

We acknowledge receipt of your amendments dated:

July 15, 2010	August 11, 2010	September 10, 2010	October 15, 2010
January 3, 2011	January 19, 2011	February 9, 2011	February 17, 2011
March 10, 2011	March 18, 2011	March 24, 2011 (2)	April 4, 2011
April 21, 2011	April 28, 2011	May 12, 2011	June 7, 2011
June 23, 2011	July 13, 2011	July 15, 2011	

These Prior Approval supplemental new drug applications provide for the expansion of the initial monotherapy indication for Topamax® (topiramate) in patients down to 2 years of age with partial onset or primary generalized tonic-clonic seizures. These supplemental applications are submitted as responses to the post-marketing commitment (PMC No. 1369-1) under the Pediatric Research Equity Act (PREA), described in our letter dated June 29, 2005.

We have completed our review of these supplemental applications, as amended. They are 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 and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under 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 note that you have fulfilled the pediatric study requirement (PMC No. 1369-1) for all relevant pediatric age groups for these applications.

We note that, on June 29, 2005, we approved use of topiramate as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures. In addition, as part of that action under NDA 020505/S-018 and NDA 020844/S-015, we waived the pediatric study requirement for initial monotherapy in patients with partial seizures or primary generalized tonic clonic seizures ages birth up to 2 years.

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.

Since Topamax® (topiramate) was approved on December 24, 1996, we have become aware of pediatric monotherapy clinical trial data showing a risk for metabolic acidosis, and a recent publication by Zhang *et al.* (Chin J Contemp Pediatr, 2010, 12 (2):96-98) suggesting that there may be objectively measured reductions in bone mineral density. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 the known serious risk of metabolic acidosis in pediatric patients, to assess the signal of a serious risk of decreased bone mineral density, or to identify an unexpected serious risk of renal stone formation and decreased development (*i.e.* height, weight, and sexual) that may be associated with metabolic acidosis following administration of Topamax® (topiramate).

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of metabolic acidosis in pediatric patients, to assess the signal of a serious risk of decreased bone density, or to identify an unexpected serious risk of renal stone formation and decreased development (*i.e.* height, weight, and sexual) that may be associated with metabolic acidosis following administration of Topamax® (topiramate).

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

1800- 1 A one year prospective, randomized, parallel, active-control arm trial to compare the safety of Topamax® (topiramate) with regard to metabolic acidosis, renal stone formation, bone mineral density, and development (i.e. height, weight and sexual) with that of an alternate treatment in pediatric patients ages 2 to 15 years. Dosing for this study should be based on the pediatric monotherapy dosing recommendations in the approved labeling for Topamax® (topiramate) and an expected efficacious dose for the comparator.

The timetable you submitted on July 15, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	July 2012
Clinical Trial Completion Date:	March 2018
Final Report Submission Date:	September 2018

Submit the protocol to your IND with a cross-reference letter to these NDAs. Submit the final report to your NDAs. 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) 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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials

should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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, please call Jacqueline Ware, Senior Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of 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 G KATZ
07/15/2011