CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-505/S-002
20-844/S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 20-505/S-002
NDA 20-844/S-010

R.W. Johnson Pharmaceutical Research Institute
Attention: Michael H. Kaufman
Director, Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Mr. Kaufman:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate) Tablets and Topamax (topiramate capsules) Sprinkle Capsules:

	NDA 20-505/S-002	NDA 20-844/S-010
Initial Submission:	July 31, 1997	June 7, 2001
Complete Response to Action Letter:	June 7, 2001	Not applicable
User Fee Due Date:	December 8, 2001	April 8, 2002

We also acknowledge receipt of your submissions dated July 9, 2001, July 26, 2001, August 3, 2001, and August 21, 2001 to both of these applications.

These supplemental new drug applications provide for the use of Topamax (topiramate) Tablets, Topamax (topiramate) Sprinkle Capsule as adjunctive therapy in patients 2 years and older with seizures associated with Lennox-Gastaut syndrome.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling
The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Please note that the enclosed labeling includes the changes in WARNINGS and PRECAUTIONS/Information for Patients sections pertaining to acute myopia and secondary angle closure glaucoma as agreed to in your August 21, 2001 amendments.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-505/S-002, 20-844/S-010." Approval of these submissions by FDA is not required before the labeling is used.

Promotional Material
In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Health Care Professional Letter
As we agreed, you will send a "Dear Health Care Professional" letter informing health care professionals about the labeling changes pertaining to acute myopia and secondary angle closure glaucoma. When the letter is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-505/S-002
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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 20-505/S-002

R.W. Johnson Pharmaceutical Research Institute
Attention: Michael H. Kaufman
Director, Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Mr. Kaufman:

Please refer to your supplemental new drug application dated July 31, 1997, received August 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate) Tablets.

Reference is also made to our July 30, 1998 not approvable letter, your June 7, 1999 Formal Dispute Resolution Request, and to the August 31, 1999 meeting between the Agency and representatives of R.W. Johnson.

We also acknowledge receipt of your additional correspondences dated November 12, 1998, August 19, 1999, September 9, 1999, and December 3, 1999.

This supplemental new drug application provides clinical data to support a new indication for the use of Topamax (topiramate) Tablets as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients ages 12 years and older.

Upon further review of this application, we are reversing our not approvable decision conveyed in our July 30, 1998 letter. Therefore, this application, as amended, is approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed package insert.

The enclosed labeling contains much of the text originally proposed in your July 31, 1997 supplemental application, however, some revisions have been made. We have utilized a strikeout/underline format to highlight the changes using the package insert approved on May 1, 2000 (S-005) as the base document.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*

(January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which should be individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Promotional Material

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed. This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

21 page(s) of revised draft labeling has been redacted from this portion of the review.

/s/

Robert Temple
4/13/01 07:32:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-505/S-002
20-844/S-010

NON-APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-505/S-002

JUL 30 1998

The R.W. Johnson Pharmaceutical Research Institute
Attention: Michael H. Kaufman
Associate Director, Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Mr. Kaufman:

Please refer to your supplemental new drug application dated July 31, 1997, received August 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate) Tablets 25mg, 50mg, 100mg, 200mg, 300mg, and 400mg.

We acknowledge receipt of your additional correspondence and amendments dated:

August 12, 1997	October 29, 1997	January 30, 1998
August 29, 1997	December 1, 1997	March 20, 1998
September 19, 1997	January 15, 1998	April 29, 1998

The user fee goal date for this application is August 1, 1998.

This supplemental application provides clinical data to support a new indication for the use of topiramate as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome.

We have completed the review of this supplemental application, as amended, and find the information presented is inadequate. Specifically, we have reviewed the results of Study YL, and have concluded that it does not establish the effectiveness of topiramate as a treatment for Lennox-Gastaut Syndrome. Accordingly, this supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). Our reasons are as follows.

The primary analysis plan described in the protocol does not insure that the overall experiment-wise Type I error will be controlled at the traditional two-tailed 5%.

In our view, the analysis must be performed under a grand null hypothesis of the form:

H_0: $\Delta_A = 0$ and ($\Delta_B = 0$ or $\Delta_C = 0$), which is the complement of the grand alternative hypothesis, which takes the form:

H_A: $\Delta_A \neq 0$ or ($\Delta_B \neq 0$ and $\Delta_C \neq 0$).

These hypotheses are consistent with the view that the between treatment differences for both variables B and C must be shown to be different from 0 in order for the study to be considered positive, a view consistent with the stated intent of the protocol. Analyses based on the use of a restricted null hypothesis (in which $\Delta_B = 0$ **and** $\Delta_C = 0$, as is the analysis presented in your submission of 4/29/98) are inappropriate.

We have calculated the nominal alphas necessary to protect the overall Type I error rate for various degrees of correlation of the variables under several different scenarios. In one, we have set the 3 alphas equal to each other and all comparisons are two sided. In the other, we have calculated the nominal alpha for variable A, in a two-sided test, and set the alphas at which variables B and C are to be tested equal to each other under a one-sided test. We have also calculated the point estimates of the correlations of the variables from the data. In neither of these scenarios do the p-values obtained reach the threshold for significance. This is clearly true when we choose the necessary nominal alphas based on the correlations seen in the trial, and, of course, if we assume the correlation is less than this. It is also true even if we assume the correlation is as high as 0.9.

For this reason, we have concluded that Study YL has not demonstrated the effectiveness of topiramate as a treatment for Lennox Gastaut syndrome.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

/S/

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research