CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20844, S001

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-505/S-003

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

JUL 31 1998

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 28, 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 primary generalized tonic-clonic seizures.

We have completed the review of this supplemental application, as amended, and find the information presented is inadequate. Specifically, we find the results of Studies YTC and TYCE, taken together, fail to establish the effectiveness of topiramate as a treatment for primary generalized tonic-clonic seizures. 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.

While Study YTC clearly supports the effectiveness of topiramate in this indication, Study YTCE does not. In the face of conflicting results in 2 controlled trials each capable of establishing an effect, it would be imprudent to conclude that the trial which demonstrated a statistically significant between treatment difference more accurately reflected the true state of nature than the trial that failed to demonstrate such an effect. Attempts to explain the differences (unusually high placebo response in Study YTCE, baseline differences, etc.), are post hoc explanations that carry little inferential value.

[redacted]

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.

Sincerely yours,

/S/ 7/3/9,

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 28 1998

NDA 20-505/S-001

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	

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 partial onset seizures in pediatric populations.

We have completed the review of this supplemental application, as amended, and it is approvable. We have concluded, based on the results of Study YP, taken together with the previously submitted data in adults, that topiramate is effective as adjunctive treatment of partial seizures in the pediatric population, and that the total experience in children establishes topiramate's safety in the pediatric population. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Topamax Tablet upon approval of this supplemental application. Although sections of this proposal are taken verbatim from the labeling proposed by you, other sections have been extensively revised and/or expanded to include new subsections. Please note that we have

embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label.

To facilitate review of your resubmission, please provide a highlighted or marked-up copy of draft labeling that shows the changes that are being made.

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

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your sNDA by submitting all safety information you now have regarding your new drugs. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the sNDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

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 submit one copy to this Division and two copies of both the

promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
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 applications, notify us of your intent to file amendments, 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 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.

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

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

SEP - 8 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Neuropharmacological
Drug Products - HFD #120
Attn: Document Control Room - 4008
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

NDA 20-505: S-003
TOPAMAX® (topiramate) Tablets

Please cross-refer to:
NDA 20-844/S-004
TOPAMAX® (topiramate capsules)
Sprinkle Capsules

DRAFT LABELING

Dear Sir/Madam:

Reference is being made to our pending supplemental application S-003 submitted to our approved New Drug Application 20-505 for TOPAMAX® (topiramate) Tablets on July 31, 1997 and our pending supplemental application S-004 submitted to our approved New Drug Application 20-844 for TOPAMAX® (topiramate capsules) Sprinkle Capsules on April 1, 1999. These supplemental applications provided data to support a new indication for the use of topiramate as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS).

As per Jacqueline Ware's request (FDA Project Manager) we are providing herewithin, revised draft labeling. On July 23, 1999, RWJPRI received approval for the use of topiramate as adjunctive therapy in pediatric patients ages 2 - 16 years with partial onset seizures. Information relevant to primary generalized tonic clonic seizures (as outlined in our April 1, 1999 submission to NDA 20-505/S-003 and 20-844/S-004) has been incorporated into the newly approved TOPAMAX labeling. All changes are provided by using a double underscore or a ~~strikeout~~ option to indicate additions or deletions of text, respectively. A copy of the proposed package insert (running text version only) is also being provided on diskette in MicroSoft Word 7.0 and is located in the archival copy of this submission.

If you have any question regarding this submission, please contact me at (908) 704-4756 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

The R.W. Johnson
Pharmaceutical Research Institute

Michael H. Kaufman
Associate Director
Regulatory Affairs

Desk Copy: Jacqueline Ware, Pharm.D. (HFD-120, Room 4026)

PATENT AND EXCLUSIVITY INFORMATION

For patent information regarding TOPAMAX (topiramate) please refer to our approved NDA 20-505 Item 13 (Volume 2.1) submitted on December 29, 1994 and subsequently approved on December 24, 1996.

PATENT INFORMATION

Topiramate is protected by the following:

U.S. Patent No.	Patent Type	Expiration Date	Owner
4,513,006	Drug Substance	September 26, 2003	Ortho-McNeil Pharmaceutical, Inc. Raritan, New Jersey (successor in business to McNeilab, Inc.)

DUPLICATE

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

DEC 01 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Neuropharmacological
Drug Products - HFD #120
Attn: Document Control Room - 4th Floor
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

NDA 20-505, S-001
TOPAMAX® (topiramate) Tablets

Please cross-refer to:
NDA 20-505 /S-003
TOPAMAX® (topiramate) Tablets

NDA SUPPL AMEND **NDA AMENDMENT**
Claimed Exclusivity

SE1-003 XR

Dear Sir/Madam:

Reference is made to our pending supplemental applications S-001 S-003, submitted to our approved New Drug Application 20-505 for TOPAMAX® (topiramate) Tablets on July 31, 1997. In accordance to 21 CFR § 314.50(j), we herein state that these supplemental applications upon approval by the U.S. Food and Drug Administration, are entitled to a three year period of marketing exclusivity under the provisions of 21 CFR § 314.108(b)(5). We certify that the studies upon which these supplemental applications rely are "new clinical investigations" that are "essential to approval of the supplements" and were "conducted or sponsored by the applicant" within the meaning of 21 CRF § 314.108(a)

Should you have any questions concerning this submission, please contact me directly at (908) 704-4756 or at our telephone number dedicated for FDA use (908) 704-4600.

Sincerely yours,

The. R.W. Johnson
Pharmaceutical Research Institute

CENTER FOR DRUG EVALUATION AND RESEARCH

DEC 02 1997

RECEIVED HFD-120

Michael H. Kaufman
Associate Director
Regulatory Affairs

cc: Jacqueline Ware, Pharm.D. (HFD-120, Room 4026)

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Exclusivity Summary for NDA 20-505/S-003

Exclusivity Summary Form

Trade Name: **Topamax** Generic Name: **topiramate tablets**

Applicant Name: **R.W. Johnson Pharmaceutical Research Institute**

HFD#: **HFD-120** Approval Date If Known:

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. *An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.*

a) Is it an original NDA? YES /___/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/
If yes, what type? (SE1, SE2, etc.) **SE1**

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

---

d) Did the applicant request exclusivity? YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
The applicant requested 3 years of marketing exclusivity.

e) Has pediatric exclusivity been granted for this Active Moiety? **NO**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO- please indicate as such) YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-505/S-003

3. Is this drug product or indication a DESI upgrade? YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety. YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-505 Topamax (topiramate) Tablets

2. Combination product – **not applicable**

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

APPEARS THIS WAY
ON ORIGINAL

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cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-505/S-003

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) **If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a).** If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. YES /_X_/ NO/___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? YES /_X_/ NO/___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? YES /___/ NO/_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. YES /___/ NO/_X_/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? YES /___/ NO/_X_/

If yes, explain: _____

(c) If the answers to (b)(1) and (h)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: **Trial YTC**

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cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-505/S-003

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/ Investigation #2 YES /___/ NO /___/ .

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/ Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on: _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): **Trial YTC**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 **Trial YTC** IND #(_____) YES /_X_/ NO /___/

If no, explain: _____

Investigation #2 IND #_____ YES /___/ NO /___/

If no, explain: _____

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cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-505/S-003

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **Not applicable.**

Investigation #1 IND # YES /___/ NO /___/

If no, explain: _____

Investigation #2 IND # _____ YES /___/ NO /___/

If no, explain: _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) YES /___/ NO /_X_/

If yes, explain: _____

Signature: _____ ***Date:*** 10/1/99

Title: Project Manager

Signature of Office/Division Director

Signature: _____ ***Date:*** 10/1/99

Russell Katz, M.D., Acting Director, HFD-120

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-844/S-004

Exclusivity Summary Form

Trade Name: **Topamax Sprinkle Capsules** Generic Name: **topiramate capsules**

Applicant Name: **R.W. Johnson Pharmaceutical Research Institute**

HFD#: **HFD-120** Approval Date If Known: OCT 1 [illegible]

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. *An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.*

a) Is it an original NDA? YES /___/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/
If yes, what type? (SE1, SE2, etc.) **SE1**

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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d) Did the applicant request exclusivity? YES /__/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? **NO**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO- please indicate as such) YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-844/S-004

3. Is this drug product or indication a DESI upgrade? YES /___/ NO/_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety. YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-844 Topamax (topiramate capsules) Sprinkle Capsules

2. Combination product – **not applicable**

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Summary for NDA 20-844/S-004

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) **If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a).** If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. YES /_X_/ NO/___/

NDA 20-844/S-004 contains clinical investigations by right of reference to clinical investigations contained in NDA 20-505/S-003. No new or additional clinical data was submitted in NDA 20-844/S-004.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? **Skipped to 3(a)** YES /__/ NO/___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? **Skipped to 3(a)** YES /__/ NO/__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. YES /___/ NO/___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? YES /___/ NO/___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Exclusivity Summary for NDA 20-844/S-004

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/ Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/ Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on: _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): **Trial YTC**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 Trial YTC IND #[redacted] YES /_X_/ NO /___/

If no, explain: _____

Investigation #2 IND #_____ YES /___/ NO /___/

If no, explain: _____

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-844/S-004

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **Not applicable.**

Investigation #1 IND # YES /___/ NO /___/

If no, explain: _____

Investigation #2 IND #_____ YES /___/ NO /___/

If no, explain: _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) YES /___/ NO /_X_/

If yes, explain: _____

Signature: /S/ ***Date:*** 10/1/99

Title: Project Manager

Signature of Office/Division Director

Signature: /S/ ***Date:*** 10.1.99

Russell Katz, M.D., Acting Director, HFD-120

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20505	**Trade Name:**	TOPAMAX (TOPIRAMATE) ORAL TABS 100MG/200
Supplement Number:	3	**Generic Name:**	TOPIRAMATE
Supplement Type:	SE1	**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP	**Proposed Indication:**	The use of topiramate as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

___NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
___Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Application approved 10/1/99.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JACKIE WARE

/S/
Signature

10/1/99
Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20844	**Trade Name:**	TOPAMAX(TOPIRAMATE)SPRINKLE CAPS 50/25/1
Supplement Number:	4	**Generic Name:**	TOPIRAMATE
Supplement Type:	SE1	**Dosage Form:**	Capsule, Coated Pellets; Oral
Regulatory Action:	AP	**Proposed Indication:**	The use of topiramate as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_Children (25 months-12 Years)
____Infants (1-24 Months) _X_Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Application approved 10/1/99.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JACKIE WARE

/S/ _____ 10/1/99

Signature Date

DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute certifies that we did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or 306 (b) of the Federal Food Drug and Cosmetic Act in connection with this suppemental New Drug Application.

ITEM 16: DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Michael H. Kaufman

Michael H. Kaufman
Associate Director, Regulatory Affairs
The R.W. Johnson Pharmaceutical Research Institute
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

APPEARS THIS WAY
ON ORIGINAL

PROJECT MANAGER LABELING REVIEW

Applications Reviewed/Date Submitted:

NDA 20-505/S-001	January 29, 1999 (Response to FDA Approvable Letter) July 31, 1997 (Initial submission)
NDA 20-505/S-004	December 16, 1997 (Initial submission)
NDA 20-505/S-006	March 9, 1999 (Initial submission)
NDA 20-844/S-001	January 29, 1999 (Initial submission)
NDA 20-844/S-003	March 9, 1999 (Initial submission)

Products:

NDA 20-505	Topamax (topiramate) Tablets
NDA 20-884	Topamax (topiramate capsules) Sprinkle Capsules

Sponsor:
R.W. Johnson Pharmaceutical Research Institute

Description of Application:

Application	Description
NDA 20-505/S-001 NDA 20-844/S-001	Provide for a new indication – use of topiramate as adjunctive therapy in the treatment of partial onset seizures in pediatric populations.
NDA 20-505/S-004	Provides for addition of the Sudden Unexplained Death in Epilepsy subsection to the WARNINGS section. (Submitted as a CBE at our request because subsection was inadvertently omitted for the original approved labeling for topiramate tablets).
NDA 20-505/S-006 NDA 20-844/S-003	Provide for addition of a new final paragraph in the Pregnancy subsection of the PRECAUTIONS section. Specifically, this paragraph describes cases of hypospadias reported during post-marketing experience. (Submitted as a CBE to improve safe use of topiramate.)

Description of Materials Reviewed:

The base document for this labeling comparison (Attachment 1) was the approvable draft labeling for NDA 20-505/S-001, issued July 28, 1998, (Attachment 2) [S001.AELBL]. S001.AELBL was electronically compared to 1) the sponsor's draft labeling submitted as a response to our approvable letter, on January 29, 1999, to NDA 20-505/S-001 and NDA 20-884/S-001 (Attachment 3) [RWJ.AZLBL] **and** 2) the sponsor's approved labeling for NDA 20-884, approved October 26, 1998 (Attachment 4) [TOPCAP.APLBL] using

Microsoft Word 97 and its "Compare Documents" tool. Deletions to S001.AELBL were indicated by "strikeout" text and additions by "underline" text. Revisions are either printed in red or blue ink (no difference between the 2 colors). Each revision to S001.AELBL was numbered and a corresponding numbered description of the revision was provided at the end of the comparison document.

Of note, regarding RWJ.AZLBL, was that the proposed topiramate labeling was a combined package insert for both the tablet and the sprinkle capsule formulation. This manipulation by the sponsor was what necessitated the additional electronic comparison to TOPCAP.APLBL.

The proposed text for the SUDEP subsection, submitted in NDA 20-505/S-004, was included in S001.AELBL at the time it was issued to the firm. The text of this subsection has been reviewed by the division although no formal approval letter has yet issued for this supplement (see attached letters dated 9/19/97 and 12/16/97 – Attachment 5).

The proposed paragraph regarding cases of hypospadias, submitted in NDA 20-505/S-006 and NDA 20-844/S-003 (Attachment 6, Attachment 7- Dr. Tresley's review of these supplements), has been manually added to the labeling comparison document. Since it is new text as compared to S001.AELBL, it was also indicated by "underline" text.

To summarize, deleted text to S001.AELBL was indicated by "strikeout" text and new text by "underline" text. The sources of the new text were RWJ.AZLBL, TOPCAP.APLBL, and the hypospadias paragraph. The exact source of the new text was identified in the numbered endnote corresponding to the numbered revision.

Conclusions:

1. There are 52 revisions that have been made to S001.AELBL.

2. Revisions 1-3, 5-9, 11-23, 25-31, 33-37, 40-45, and 47-52 are either editorial additions/deletions, improvements in clarity of text, changes for completeness due to combining the tablet and sprinkle labeling, or modifications so that labeling conforms with approved sprinkle text.

3. Revisions 4, 10, 24, 32, 38, 39, and 46 require review and assessment by a member of the division's review team.

Additional Comments:

1. The clinical team should consider changing the word [redacted]' in the INDICATIONS, Cognitive/Neuropsychiatric Adverse Events subsection of WARNINGS, and DOSAGE AND ADMINISTRATION sections to "pediatric patients" or something similar. The reason is tha[redacted], as defined by FDA pediatric age range definitions, includes patients ages 2-12 years. The age range of pediatric patients studied for the new indication includes adolescents ages 12-16 years. Therefore, technically, "children" does not adequately describe the population studied.

   Places where[redacted]" is used in the labeling is indicated by yellow highlighting.

2. In a reviews dated 10/27/98 (Attachment 8) and 2/23/99 (Attachment 9), Dr. Tresley, the clinical reviewer for topiramate, recommends the addition of a "Postmarketing and Other Experience" subsection to the ADVERSE REACTIONS section. Specifically, the new subsection would describe hepatic events reported in patients receiving topiramate during post-marketing experience. Also Dr. Tresley recommends that the WARNINGS section of labeling "advise regular monitoring of SGOT, SGPT, and bilirubin while patients are on Topamax", the SUDEP rate be[redacted]based on Final Safety Update, and additional treatment emergent adverse events should be added to the pediatric list. These recommendations should be considered prior to taking an action on NDA 20-505/S-001.

Recommendation:

With concurrence from the division director, an approval letter should issue for all of the above supplements once acceptable labeling has been negotiated.

/S/ 7/9/99

Jacqueline H. Ware, Pharm.D. Date
Project Manager

/S/ 7/9/99

John S. Purvis Date
Chief, Project Management Staff

APPEARS THIS WAY
ON ORIGINAL

30 Pages

DRAFT

LABELING

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-844

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

OCT 26 1998

Dear Mr. Kaufman:

Please refer to your new drug application (NDA) dated July 31, 1997, received August 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Topamax (topiramate capsules) Sprinkle Capsules 15mg, 25mg, and 50mg.

We acknowledge receipt of your additional correspondence and amendments dated July 21, 1998, and August 26, 1998. Your submission of August 26, 1998 constituted a full response to our July 20, 1998 action letter.

The user fee goal date for this application is October 27, 1998.

This new drug application provides for a sprinkle capsule formulation of topiramate, a new dosage form, as adjunctive therapy for the treatment of adults with partial onset seizures.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted August 26, 1998, patient package insert submitted August 26, 1998, immediate container and carton labels submitted August 26, 1998) with the revisions listed below. Accordingly, the application is approved effective on the date of this letter.

1. The second sentence of the Oral Contraceptives subsection in the PRECAUTIONS section of the package insert has been revised to the following:

   The mean oral clearance of ethinyl estradiol at 800 mg/day dose was increased by 47% (range: 13- 107%).

   We note that you have agreed to this revision as per the October 7, 1998 telephone conversation between Catherine Glamkowski of R.W. Johnson Pharmaceutical Research Institute and Jacqueline Ware of this Division.

2. References to the 50 mg capsule strength of topiramate have been added to the DESCRIPTION and HOW SUPPLIED sections of the package insert.

   We note that your August 26, 1998 submission advised that references to the 50 mg capsule strength of topiramate were removed from proposed labeling because this strength would not be marketed at this time. However, given that this letter provides an approval action for this application, we are including reference to the 50 mg capsule strength for completeness. It is acceptable to remove reference to the 50 mg capsule strength of topiramate from your final printed labeling.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case 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, this submission should be designated "FPL for approved NDA 20-844." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product (containers and cartons only) when it is available.

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, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

/S/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-505

The R.W. Johnson
Pharmaceutical Research Institute
Attention: Michael Kaufman
P.O. Box 300
Raritan, NJ 08869-0602

SEP 19 1997

Dear Mr. Kaufman:

Please refer to your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Topamax® (topiramate) tablets.

Reference is also made to a letter dated August 25, 1997, which proposed "Sudden Unexplained Death in Epilepsy" (SUDEP) text to be included under the WARNINGS section of product labeling.

We have completed our review of your proposal and request that the following text for a SUDEP section, under WARNINGS, be submitted as final printed labeling in the form of a "SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED" as described under 21 CFR 314.70(c).

> During the course of premarketing development of TOPAMAX® (topiramate), 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).
>
> This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX program, to 0.005 for patients with refractory epilepsy).

Please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

This change should be implemented within three months.

M. H. Kaufman

SEP 23 1997

Should you have any questions, please contact Jacqueline Ware, Pharm. D., Regulatory Management Officer, at (301) 594-5793.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

DEC 16 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Neuropharmacological
Drug Products - HFD #120
Attn: Document Control Room - 4th Floor
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

NDA 20-505 SLR-004
TOPAMAX® (topiramate) Tablets

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED
Final Printed Labeling

Dear Sir/Madam:

Reference is made to our New Drug Application 20-505 for TOPAMAX® (topiramate) Tablets and to the Division's letter dated July 1, 1997 that requested draft text for a new section entitled "Sudden Unexplained Death in Epilepsy" (SUDEP) to be added under the WARNINGS heading of our current product labeling. Reference is also made to our August 25, 1997 submission that provided proposed language for the SUDEP statement and to the Division's September 19, 1997 letter (copy attached) that accepted our draft text with minor revisions.

In accordance with 21 CFR 314.70(c) we are submitting Final Printed Labeling for the Physician Insert. The Physician Insert (code # 643-10-443-2) has been modified to include information on sudden unexplained death in epilepsy. In addition, the following two headings listed under the WARNINGS section have been underscored for consistency purposes; Withdrawal of AEDs and Cognitive/Neuropsychiatric Adverse Events.

The new section entitled "Sudden Unexplained Death in Epilepsy" (SUDEP) that has been added under the WARNINGS heading contains the following text:

> During the course of premarketing development of TOPAMAX® (topiramate), 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).
>
> This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX program, to 0.005 for patients with refractory epilepsy).

DEC 16 1997

Attached are sixteen copies of the final printed labeling (10 mounted, 6 unmounted) in a blue Archival binder. The revised TOPAMAX (topiramate) Tablet physician insert will be implemented at the next production run scheduled for January 1998.

Should you have any questions concerning this submission, please contact me directly at (908) 704-4756 or our phone number dedicated for FDA use at (908) 704-4600

Sincerely yours,

The R.W. Johnson
Pharmaceutical Research Institute

Michael H. Kaufman
Associate Director
Regulatory Affairs

cc: Jacqueline Ware, Pharm.D. (HFD-120, Room 4026)

Ware

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
U.S. HIGHWAY 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

MAR 0 9 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Neuropharmacological
Drug Products - HFD #120
Attn: Document Control Room - 4008
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

NDA 20-505
TOPAMAX® (topiramate) Tablets

Please cross-refer to:

NDA 20-844
TOPAMAX® (topiramate capsules)
Sprinkle Capsules

LABELING SUPPLEMENT:
CHANGES BEING EFFECTED
21 CFR 314.70 (c)(2)(i)

Dear Sir/Madam:

Reference is made to our New Drug Applications 20-505 and 20-844 for TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules, respectively. To date, The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) has received four reports of hypospadias following first trimester exposure to topiramate. In three of these cases, the concomitant use of carbamazepine was noted. Please note, all of these reports have been filed to the FDA as 15-day expedited safety reports.

The Medwatch Mfr. report numbers (MCN), abnormalities reported, concurrent antiepileptic drugs (AEDs), and report sources are shown below:

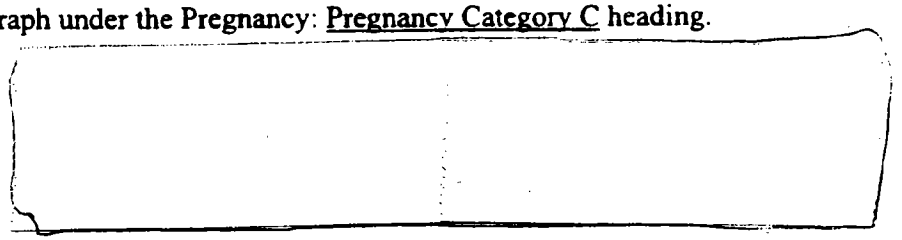
MCN	Abnormality Reported	Concurrent AEDs	Report Source
980211-107010482	Hypospadias	No AEDs	AED registry US case
980708-107012446	Hypospadias One kidney	Lamotrigine Carbamazepine	AED registry US case
980728-016012674	Hypospadias	Lamotrigine Carbamazepine Clobazam	Australia
980806-005012850	Hypospadias	Carbamazepine	UK

Non-clinical reproductive toxicology studies of topiramate in mice, rats, and rabbits have shown no teratogenic effect on the urogenital system; the observed teratogenic effects, principally skeletal, were consistent with those seen with other carbonic anhydrase inhibitors.

Hypospadia is a relatively common birth defect per se, and is a feature of antiepileptic drug embryopathy. However, the frequency of hypospadias in the background population and among pregnancies in epileptic women is not easily obtainable. In a 1972 - 1973 systematic examination of 7,157 newborn infants at the Boston Lying-In Hospital (now part of the Brigham and Women's Hospital), the prevalence rate of hypospadias was 8/1000. Based on sale figures since the launch of TOPAMAX, approximately 180,000 patients worldwide have used topiramate, with an average duration of 6 months. The annual pregnancy rate in American and Western European populations as a whole is slightly less than 1% so an estimate of the number of topiramate exposed pregnancies would be 180,000 x ½ x 0.01 = 900. Thus by chance association we would expect the occurrence of about 8 cases of hypospadias in the male offspring of pregnant women exposed to topiramate.

The four cases of hypospadias reported to RWJPRI may therefore be chance occurrences. However, it is recognized that spontaneous adverse events are under reported. As the normal ratio of hypospadias to other birth defects is about 1/10; the company appears to have a disproportionate number of hypospadias in its database although this finding may also be due to biases in reporting or to the co-administration of other AEDs. Since we cannot exclude the possibility of hypospadia's association with topiramate we are updating our labeling for TOPAMAX to make physicians aware of this birth defect. Reports of all birth defects will continue to be closely monitored by RWJPRI's pharmacovigilance systems in addition to using the AED pregnancy register to collect information on malformations occurring among topiramate exposed infants.

In accordance with 21 CFR 314.70(c)(2)(i) we are submitting the following text to be added to the PRECAUTIONS section of our current product labeling after the last paragraph under the Pregnancy: Pregnancy Category C heading.



Since the labeling revision only effects the Pregnancy: Pregnancy Category C section of the package insert, which is the same in both the TOPAMAX Tablet and Sprinkle Capsule inserts, this submission is being cross-referenced in it's entirety to NDA 20-844.

We are currently in the process of updating our labeling to include the statement on hypospadias and will implement this change within 90 days. Final printed labeling will be submitted to the Agency when available.

Should you have any questions concerning this submission, please contact me directly at (908) 704-5360 or our phone number dedicated for FDA use at (908) 704-4600.

Sincerely yours,

The R.W. Johnson
Pharmaceutical Research Institute

Catherine M. Glamkowski

Catherine M. Glamkowski
Principal Regulatory Scientist
Regulatory Affairs

cc: Jacqueline Ware, Pharm.D. (HFD-120, Room 4026)

62 Pages

DRAFT

LABELING

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-505/S-003
NDA 20-844/S-004

OCT 1 1999

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 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-003	NDA 20-844/S-004
Initial Submission:	July 31, 1997	April 1, 1999
Complete Response to Action Letter:	April 1, 1999	n/a
User Fee Due Date:	October 2, 1999	January 2, 2000

These supplemental new drug applications provide for the use of Topamax (topiramate) Tablets and Topamax (topiramate capsules) Sprinkle Capsules as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures.

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 enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. 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-003, 20-844/S-004." Approval of these submissions by FDA is not required before the labeling is used.

Promotional Material

In addition, if you have not already done so, 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 submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Other

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" 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, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

/S/

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

Enclosure

PROJECT MANAGER LABELING REVIEW

Applications Reviewed/Date Submitted:

NDA 20-505/S-003	April 1, 1999 (Response to FDA Not Approvable Letter) July 31, 1997 (Initial submission)
NDA 20-844/S-004	April 1, 1999 (Initial submission)

Products:

NDA 20-505	Topamax (topiramate) Tablets
NDA 20-884	Topamax (topiramate capsules) Sprinkle Capsules

Sponsor:
R.W. Johnson Pharmaceutical Research Institute

Description of Application:

Application	Description
NDA 20-505/S-003 NDA 20-844/S-004	Provide for a new indication – use of topiramate in the treatment of primary generalized tonic clonic seizures.

Description of Materials Reviewed:

The base document for this labeling comparison (Attachment 1) was the approved labeling NDA 20-505/S-001 & NDA 20-844/S-001, issued July 23, 1999, (Attachment 2) [S001.APLBL]. S001.APLBL was electronically compared to 1) the sponsor's draft labeling submitted as a minor labeling amendment on September 8, 1999, to NDA 20-505/S-003 and NDA 20-884/S-004 (Attachment 3) [RWJ.REVLBL] using Microsoft Word 97 and its "Compare Documents" tool. Deletions to S001.APLBL were indicated by "strikeout" text and additions by "underline" text. Revisions are either printed in red. Each revision to S001.APLBL was numbered and a corresponding numbered description of the revision was provided at the bottom of the page that contained the revision.

1 Page REDACTED

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2. Revisions 1-7 require review and assessment by a member of the division's review team.

3. Revision 8 is an editorial additions due to reorganization within the firm.

Additional Comments:

1. Careful consideration should be given to revisions 4 and 7 that state the indications for which topiramate is approved. As currently proposed by the sponsor, the sentence implies that topiramate is effective for adults and pediatrics with either partial seizures or generalized tonic clonic seizures. This project manager is not sure if the clinical studies for generalized tonic clonic seizures included pediatric patients 2 to 16 years of age. The clinical reviewer should evaluate this.

Recommendation:

With concurrence from the division director, an approval letter should issue for the above supplements once acceptable labeling has been negotiated.

/S/ 9/21/99

Jacqueline H. Ware, Pharm.D. Date
Project Manager

/S/ Grace J. Pina 9/22/99

John S. Purvis Date
Chief, Project Management Staff

APPEARS THIS WAY
ON ORIGINAL

62 Pages

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