

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020844

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20-844

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>completed</u>
INITIAL SUBMISSION:	31-JUL-97	01-AUG-97	14-AUG-97	31-DEC-97
AMENDMENT:	26-AUG-98	27-AUG-98	01-SEP-98	08-SEP-98

CHEMIST REVIEW: #4

SPONSOR: R.W. JOHNSON PHARMACEUTICAL
RESEARCH INSTITUTE

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 920 Route 202 South, P.O.Box 300
Raritan, N.J. 08869-0602

PRODUCT NAME:

Proprietary:

Topamax Sprinkle Capsules

USAN [1987]:

Topiramate

Code Name/Number:

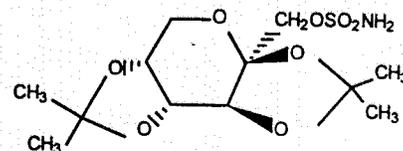
RWJ-17021

Established Name:

topiramate capsules

DOSAGE FORM/ROUTE OF ADMINISTRATION: 15, 25, 50-mg coated
beads per capsule/oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy



STRUCTURAL FORMULA & CHEMICAL NAME:

C₁₂H₂₁NO₈S Mol. Wt. 339.37 [CAS Number 97240-79-4]

2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate

REMARKS: In this amendment the firm responds to the CMC deficiencies in the Approvable letter dated July 20, 1998. The firm also agrees on the changes recommended by the Labeling and Nomenclature Committee for the proprietary and established names of the drug product (see above).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-844 is APPROVED based on adequate responses to the CMC deficiencies. All site inspections are completed and received satisfactory recommendations from the Office of Compliance. An Expiry date of 24 months is acceptable and is supported by real time stability data. The firm agreed to Biopharmaceutics recommendation of a dissolution specification "_____ (Q) in _____ minutes, with _____ mL _____ as medium and using USP Apparatus 2 at _____ rpm."

cc: NDA 20-844
HFD-120/Div. File

HFD-120/JWare/MGuzewska/MZarifa

HFD-810/CHolberg

1/S/ 9.9.98 INIT:

Filename: n020844.003

/S/
 Mona Zarifa, Ph.D. Chemist

JUL 10 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20-844

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>completed</u>
INITIAL SUBMISSION:	31-JUL-97	01-AUG-97	14-AUG-97	31-DEC-97
AMENDMENT:	24-JUN-98	25-JUN-98	25-JUN-98	01-JUL-98

CHEMIST REVIEW: #3

SPONSOR: R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 920 Route 202 South, P.O.Box 300 Raritan, N.J. 08869-0602

PRODUCT NAME:

Proprietary:

Topamax Sprinkle [Recommended by LNC]

USAN [1987]:

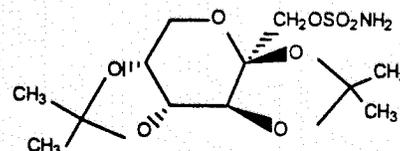
Topiramate

Code Name/Number:

RWJ-17021

DOSAGE FORM/ROUTE OF ADMINISTRATION: 15, 25, 50-mg coated beads per capsule/oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy



STRUCTURAL FORMULA & CHEMICAL NAME:

C₁₂H₂₁NO₈S Mol. Wt. 339.37 [CAS Number 97240-79-4]

2,3:4,5-Di-O-1-isopropylidene-beta-D-fructopyranose sulfamate

REMARKS: The sponsor amends the labeling for topiramate sprinkle capsules to (1) change the name of the manufacturer (s) to reflect the new corporate structure and to (2) replace the statement "Federal law prohibits dispensing without prescription" to "Rx only" in accordance to FDAMA. Note that the manufacturing sites in the NDA remain the same and that the change in labeling (1) only reflects the new marketing address.

CONCLUSIONS & RECOMMENDATIONS: As in CMC Review 2, recommend NDA 20-844 is APPROVABLE contingent upon receipt of clarification of CMC deficiencies. All site inspections are completed and received satisfactory recommendations from the Office of Compliance. An Expiry date of 24 months is acceptable and is supported by real time stability data. The Division of Biopharmaceutics recommend a dissolution specification " (Q) in minutes, with mL as medium and using USP Apparatus 2 at rpm."

cc: NDA 20-844

HFD-120/Div. File

HFD-120/JWare/MGuzewska/MZarifa

HFD-810/CHOiberg

IS/ 7.10.98 INIT:

Filename: n020844.002

Mona Zarifa, Ph.D., Chemist

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

Part 2
NDA 20-844

INITIAL SUBMISSION: letterdate 31-JUL-97 stampdate 01-AUG-97 rec'd by chemist 14-AUG-97 completed 31-DEC-97

CHEMIST REVIEW: # 2

SPONSOR: R.W. JOHNSON PHARMACEUTICAL
RESEARCH INSTITUTE

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 920 Route 202 South, P.O.Box 300
Raritan, N.J. 08869-0602

PRODUCT NAME:

Proprietary:

Topamax Sprinkle [Recommended by LNC]

USAN [1987]:

Topiramate

Code Name/Number:

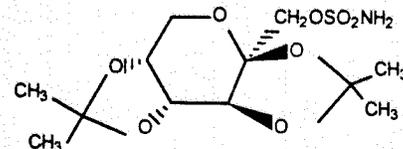
RWJ-17021

DOSAGE FORM/ROUTE OF ADMINISTRATION: 15, 25, 50-mg coated beads per capsule/oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{12}H_{21}NO_8S$ Mol. Wt. 339.37 [CAS Number 97240-79-4]



2,3:4,5-Di-O-1-isopropylidene- β -D-fructopyranose sulfamate

REMARKS: All site inspections are now completed.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-844 is APPROVABLE contingent upon receipt of clarification of CMC deficiencies. All site inspections are completed and received satisfactory recommendations from the Office of Compliance. See attached EER report. An Expiry date of 24 months is acceptable and is supported by real time stability data. The Division of Biopharmaceutics recommend a dissolution specification ' (Q) in minutes, with mL as medium and using USP Apparatus 2 at rpm."

cc: NDA 20-844

HFD-120/Div. File

HFD-120/JWare/MGuzewska/MZarifa

HFD-810/CHolberg

/S/ 6.15.98 INIT:

Filename: n020844.001

/S/
Mona Zarifa, Ph.D., Chemist

6/15/98

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
 REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS**

NDA 20-844

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>completed</u>
INITIAL SUBMISSION:	31-JUL-97	01-AUG-97	14-AUG-97	31-DEC-97
AMENDMENTS:	18-AUG-97	19-AUG-97	19-AUG-97	31-DEC-97
	29-OCT-97	30-OCT-97	30-OCT-97	31-DEC-97
	27-JAN-98	28-JAN-98	23-JAN-98	03-FEB-98
	21-APR-98	22-APR-98	22-APR-98	06-MAY-98
	05-MAY-98		05-MAY-98	06-MAY-98
	15-MAY-98	18-MAY-98	18-MAY-98	18-MAY-98
	22-MAY-98		22-MAY-98	22-MAY-98

CHEMIST REVIEW: # 1

SPONSOR: R.W. JOHNSON PHARMACEUTICAL
 RESEARCH INSTITUTE
 ADDRESS: 920 Route 202 South, P.O.Box 300
 Raritan, N.J. 08869-0602

REVIEW CHEMIST: M.Zarifa, Ph.D

PRODUCT NAME:

Proprietary:

USAN [1987]:

Code Name/Number:

Topamax Sprinkle [Recommended by LNC]
 Topiramate
 RWJ-17021

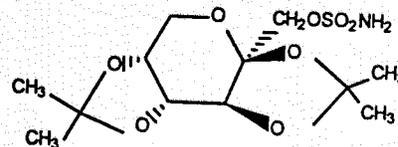
DOSAGE FORM/ROUTE OF ADMINISTRATION: 15, 25,50-mg coated beads per capsule/oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{12}H_{21}NO_8S$ Mol. Wt. 339.37 [CAS Number 97240-79-4]

2,3:4,5-Di-O-1-isopropylidene-β-D-fructopyranose sulfamate



REMARKS: The firm references NDA 20-505 (tablets) for information on the drug substance and its specifications and controls. This NDA is for a new dosage form (encapsulated sprinkles). The firm developed validated modifications of the tablets test methods to allow for testing of the sprinkle form. The firm had submitted IND) for the sprinkles.

All CMC comments and recommendations in the meeting minutes were addressed by the firm. The amendment dated August 18, 1997 provides a revised index to the NDA. The amendment dated October 29, 1997 provides a withdrawal of the Environmental Assessment replaces it with a Categorical exclusion request. The amendment dated January 27, 1998 provides updates to the analytical methods. The firm provides stability updates in the amendment dated April 21, 1998. May 5 amendment provides clarification on the control testing functions of the various sites listed in the NDA. May 15 amendment provides justification impurity level specifications. May 22 amendment provides the available batch analysis results for the sprinkle dosage form.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-844 is APPROVABLE contingent upon receipt of clarification of CMC deficiencies and completion of site inspections (Site inspections were completed and were satisfactory except for two testing sites which are pending). An Expiry date of 24 months is acceptable and is supported by real time stability data. The Division of Biopharmaceutics recommend a dissolution specification (Q) in minutes, with mL as medium and using USP Apparatus 2 at rpm." (X)

cc: NDA 20-844
 HFD-120/Div. File/JWare/MGuzewska/MZarifa
 HFD-810/Choiberg

/S/
 Mona Zarifa, Ph.D., Review Chemist

Filename: n020844.000

1111
 1/5/98
 6.8.98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020844

PHARMACOLOGY REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 30, 1998

FROM: Glenna G. Fitzgerald, Ph.D. /S/
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-844
Topamax (topiramate capsules) Sprinkle Capsules
Sponsor: R.W. Johnson Pharmaceutical Research Institute

SUBJECT: Approvability

There were no preclinical studies submitted to this NDA for a new formulation for Topamax and there are no unusual excipients in the new formulation. The pharmacology and toxicology studies submitted to NDA 20-505 for Topamax tablets support approval of the sprinkle dosage form and no additional studies are needed.

APPEARS THIS WAY
ON ORIGINAL