DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,505

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	29-DEC-94	30-DEC-94	3-JAN-95	27-MAR-95

CHEMIST REVIEW: # 1

REVIEW CHEMIST: M.Zarifa, Ph.D

SPONSOR: R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

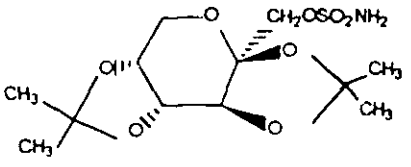
ADDRESS: Welsh & McKean Roads
Spring House, PA 19477

PRODUCT NAME:

Proprietary:	TOPAMAX™ topiramate
USAN:	none
Code Name/Number:	**RWJ-17021**
Other:	Topiramate; Topiramat

MAY 31 1995

DOSAGE FORM/ROUTE OF ADMINISTRATION: 100 mg, 200 mg,



PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{12}H_{21}NO_8S$ **Mol. Wt.** 339.36

2,3:4,5-Bi-O-(1-methylethylidene)-β-D-fructopyranose sulfamate [CAS Registry Number 97240-79-4]

REMARKS: The n.d.s. is a D-fructopyranose derivative. It is soluble in water with marked increase in solubility in alkaline media and in the presence of cosolvents like PEG 400. It is a weak acid having low ionization potential and its partition favors the organic phase over the aqueous phase. All through the application there are variations across the studies in the source of the n.d.s. and the site of manufacturing of the drug product. The sponsor, however presents sufficient data to support there are no significant differences in impurity and dissolution profiles across these batches. The degradation of the n.d.s. in solid form is accelerated by heat and humidity and in solution it hydrolyses in low pH acid media to fructose and its subsequent degradation products. The sponsor is proposing an expiration date of 24 months. The application contains deficiencies regarding the n.d.s. manufacturing, n.d.s. and drug product specifications, and specifications for the coating materials. Also, the provided stability commitment statement was found unacceptable.

CONCLUSIONS & RECOMMENDATIONS: Methods validation packages are on hand. Methods validation request will be sent. Environmental Assessment has been requested. Establishment inspection has been requested.

RECOMMEND THAT **NDA 20-505 FOR TOPIRAMATE TABLETS IS NOT APPROVABLE.** SATISFACTORY CORRECTION OF CMC DEFICIENCIES IS REQUIRED. **SEE CMC DEFICIENCY LETTER.**

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/J.Purvis
HFD-120/SBlum/MZarifa
INIT:

filename: N020505.000

5/31/95

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,505

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	29-DEC-94	30-DEC-94	3-JAN-95	27-MAR-95
AMENDMENT:	10-MAY-95	11-MAY-95	18-MAY-95	19-MAY-95

CHEMIST REVIEW: # 2

REVIEW CHEMIST: M.Zarifa, Ph.D

SPONSOR: R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

ADDRESS: Welsh & McKean Roads
Spring House, PA 19477

PRODUCT NAME:

Proprietary: TOPAMAX™ topiramate

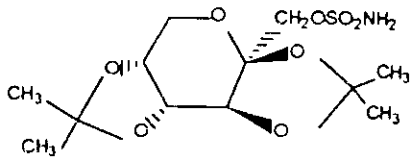
USAN: none

Code Name/Number: **RWJ-17021**

Other: Topiramate; Topiramat

DOSAGE FORM/ROUTE OF ADMINISTRATION: 25, 100, 200,

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy



STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{12}H_{21}NO_8S$ Mol. Wt. 339.36

2,3:4,5-Bi-O-(1-methylethylidene)-β-D-fructopyranose sulfamate [CAS Registry Number 97240-79-4]

REMARKS: The amendment introduces two additional dosage forms, the 25- manufactured from a common granulation that also includes the 100-mg tablet formulation. The sponsor provides adequate 6-month stability data and stability studies are on-going.
NOTES.

CONCLUSIONS & RECOMMENDATIONS:

In CMC Review #1 it was recommended that **NDA 20-505 FOR TOPIRAMATE TABLETS IS NOT APPROVABLE**. SATISFACTORY CORRECTION OF CMC DEFICIENCIES WAS REQUIRED.

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
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HFD-120/SBlum/MZarifa
INIT:

filename: N020505.001

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,505

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	29-DEC-94	30-DEC-94	3-JAN-95	27-MAR-95
AMENDMENTS:	05-OCT-95	06-OCT-95	26-OCT-95	02-NOV-95
	19-OCT-95	20-OCT-95	26-OCT-95	02-NOV-95

CHEMIST REVIEW: # 3

REVIEW CHEMIST: M.Zarifa, Ph.D

SPONSOR:

ADDRESS: R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE
Welsh & McKean Roads
Spring House, PA 19477

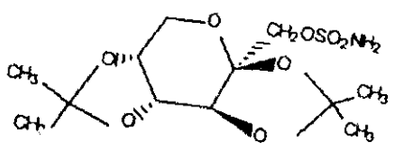
PRODUCT NAME:
Proprietary: TOPAMAX™ topiramate
USAN: none
Code Name/Number: RWJ-17021
Other: Topiramate; Topiramat

DOSAGE FORM/ROUTE OF ADMINISTRATION: 25, 100, 200,

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy

STRUCTURAL FORMULA & CHEMICAL NAME:
$C_{12}H_{21}NO_8S$ Mol. Wt. 339.36

2,3:4,5-Bi-O-(1-methylethylidene)-β-D-fructopyranose sulfamate
[CAS Registry Number 97240-79-4]



REMARKS: The amendments provide information in response to the CMC deficiency letter (June 22, 1995) and data for the two additional dosage forms (25-

CONCLUSIONS & RECOMMENDATIONS: CORRECTION OF CMC DEFICIENCIES HAS BEEN DONE. RECOMMEND THAT NDA 20-505 FOR TOPIRAMATE TABLETS IS APPROVABLE AND APPROVED CONTINGENT UPON RECEIPT OF APPROVABLE RECOMMENDATION FROM COMPLIANCE AND EA REPORT. THE PROPOSED EXPIRY DATE IS ACCEPTABLE.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/J.Purvis
HFD-120/SBlum/MZarifa
INIT:

MB 11/22/95

filename: N020505.002

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20,505**

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	**29-DEC-94**	**30-DEC-94**	**3-JAN-95**	**27-MAR-95**
AMENDMENTS:	**20-NOV-95**	**21-NOV-95**	**11-DEC-95**	**11-DEC-95**

CHEMIST REVIEW: # 4

REVIEW CHEMIST: M.Zarifa, Ph.D

SPONSOR: **R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE**

ADDRESS: **Welsh & McKean Roads Spring House, PA 19477**

PRODUCT NAME:

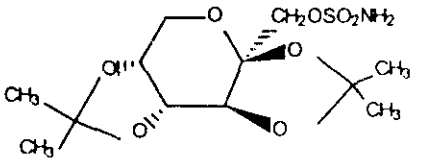
Proprietary:	TOPAMAX™ topiramate
USAN:	none
Code Name/Number:	**RWJ-17021**
Other:	Topiramate; Topiramat

DOSAGE FORM/ROUTE OF ADMINISTRATION: 25, 100, 200,

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{12}H_{21}NO_8S$ **Mol. Wt.** 339.36



2,3:4,5-Bi-O-(1-methylethylidene)-β-D-fructopyranose sulfamate
[CAS Registry Number 97240-79-4]

REMARKS: This amendment provides clarification that for the revised regulatory specifications of the

Adequate justification for this action is provided in the NDA. See NDA Vol. 4 pp. 439-448 for details.

CONCLUSIONS & RECOMMENDATIONS: CORRECTION OF CMC DEFICIENCIES HAS BEEN DONE. EER RECOMMENDATION FROM COMPLIANCE IS "ACCEPTABLE." RECOMMEND THAT **NDA 20-505 FOR TOPIRAMATE TABLETS IS APPROVED. THE PROPOSED EXPIRY DATE IS ACCEPTABLE.**

Mona Zarifa

Mona Zarifa, Ph D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/J.Purvis
HFD-120/SBlum/MZarifa
INIT:

filename: N020505.003

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20,505**

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	**29-DEC-94**	**30-DEC-94**	**3-JAN-95**	**27-MAR-95**
AMENDMENT:	**27-JUN-96**	**28-JUN-96**	**01-JUL-96**	**11-JUL-96**

CHEMIST REVIEW: # 5 **SPONSOR:** **R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE**

REVIEW CHEMIST: M.Zarifa, Ph.D **ADDRESS:** **Welsh & McKean Roads Spring House, PA 19477**

PRODUCT NAME:

Proprietary: TOPAMAX™ topiramate

USAN: none

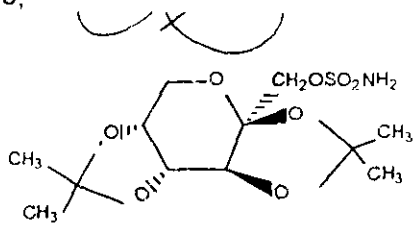
Code Name/Number: **RWJ-17021**

Other: Topiramate; Topiramat

DOSAGE FORM/ROUTE OF ADMINISTRATION: 25, 100, 200,

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Epilepsy

STRUCTURAL FORMULA & CHEMICAL NAME:



$C_{12}H_{21}NO_8S$ **Mol. Wt.** 339.36

2,3:4,5-Bi-O-(1-methylethylidene)-β-D-fructopyranose sulfamate

REMARKS: The amendment responds to the "Approvable" letter (Dec 29, 1995). The sponsor amends the dissolution method to reduce the sampling time to 20 minutes and amends the dissolution specification to in 20 minutes". The sponsor provides revised annotated versions of package and insert labeling in accordance to the Approvable letter. In addition, the sponsor revises the "Appearance" specification for each tablet strength to provide identification of the product by the trade name TOPAMAX and tablet strength instead of the marketing company's logo and NDC code. This change is also incorporated in the revised labeling.

CONCLUSIONS & RECOMMENDATIONS: The sponsor's responses are adequate. In CMC Review #4 the recommendation was that **NDA 20-505 FOR TOPIRAMATE TABLETS IS APPROVED. THE PROPOSED EXPIRY DATE IS ACCEPTABLE.**

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/J.Purvis
HFD-120/SBlum/MZarifa
INIT:

filename: N020505.004

The pharmacokinetics of topiramate was affected by renal impairment. Oral clearance decreased by 56% in the severe group (creatinine clearance <30 ml/min/1.73m^2) and by 46% in the moderate group (creatinine clearance 30-69 ml/min/1.73m^2) as compared to normals. Topiramate was effectively removed from the plasma by hemodialysis. Over 3 hours of hemodialysis about 19 mg of topiramate was removed from the body. In subjects with moderate to severe hepatic impairment, both C_{max} and AUC of topiramate increased by 29%, whereas its apparent clearance decreased by 29%.

Administration of topiramate (100-400 mg q 12h) with phenytoin (130-300 mg q 12h or 360-480 mg q 24h) led to a 20% decrease in total and free phenytoin clearance, whereas topiramate clearance increased by 2.5 fold. Carbamazepine (CBZ) (300-800 mg q 8h) given with topiramate (100-400 mg q 12h), was unaffected as was its epoxide but topiramate clearance increased two fold. Concomitant administration of valproic acid (VPA) (500-2250 mg b.i.d.) with topiramate(100-400 mg q 12h) resulted in a 13% increase in VPA clearance as well as a 15% increase in topiramate clearance. In another study involving phenytoin-Topiramate and valproic acid-Topiramate, oral clearance of topiramate was about 2.4 fold higher in patients receiving phenytoin than those receiving valproic acid, though renal clearance was unchanged in both the groups. The percent of topiramate dose excreted in urine was almost two fold higher in the group of patients who received concomitant valproic acid than the group receiving phenytoin. This may suggest that there is an increase in the metabolic clearance of topiramate in the presence of phenytoin. A single dose of digoxin increased its clearance by 13% in the presence of steady state topiramate.

In three multicenter clinical studies designed to compare the safety and efficacy of different doses of topiramate (200-1000 mg/day) in patients with refractory partial epilepsy, the median percent reduction in seizure rate was seen to increase with increasing plasma topiramate concentrations up to 5.2 µg/mL. At plasma topiramate concentrations above 5.2 µg/mL, a decrease from the peak seizure rate reduction was observed.

The Sponsor has established linkage between Phase II and Phase III tablet formulations. The Phase III tablet formulation was the same for pharmacokinetic and clinical studies and will also be the marketed formulation. Dissolution in water using paddle at 50 rpm is rapid as individual units for the biobatches show > than dissolved in 20 minutes.

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Division of Biopharmaceutics. Detailed study reports are available in the Division of Biopharmaceutics.

Comments:

1.The Sponsor is requested to incorporate 'pharmacokinetic labelling' as outlined in the Labelling section.

2. Based upon data provided by the Sponsor, the Division of Biopharmaceutics is setting the following methodology and specification for all strengths of topiramate tablets;

Please convey Comments 1 and 2 to the Sponsor.

Table of Contents

TOPIRAMATE SUMMARY

Absorption:

Absorption of oral doses of topiramate is rapid, with peak plasma concentration of 27 µg/ml occurring at approximately 2 hours following 400 mg oral doses every 12 hours. The relative bioavailability of topiramate from a 100 mg tablet is approximately 82% compared to a 100 mg oral dose of an aqueous solution.

Distribution:

The volume of distribution (V/F) of topiramate following 100 to 1200 mg oral doses ranged from 0.55 l/kg to 0.8 l/kg. Topiramate is poorly bound to human plasma proteins. Over the clinically relevant plasma concentration range of up to 33 µg/mL (in-vitro drug concentration ranged from 1 to 250 µg/mL), topiramate is approximately 17% bound to plasma proteins. A low capacity binding site for topiramate in erythrocytes is present. At topiramate concentrations (<4 µg/mL), a major portion of circulating topiramate is bound to erythrocytes. This binding was saturated at concentrations above 4 µg/ml.

Metabolism:

The metabolism of topiramate has been investigated in humans. Unchanged topiramate plus six trace metabolites (each <5% of the sample) were isolated, characterized and identified from the plasma, urine, and feces of humans. The proposed pathways of these metabolites are hydroxylation, hydrolysis and glucuronidation.

A total of 81.3 ± 4.3% of the administered dose was recovered in excreta in 10-day period. In urine 80.6 ± 4.3% of the dose was excreted, whereas only 0.72 ± 0.3% of the dose was excreted in feces. Unchanged topiramate accounted for 70% of the radioactivity in urine.

In vitro incubations of topiramate (0.5 μM-1 mM) were conducted in human liver microsomes. With $CYP2C_{meph}$ isozyme, 4'-OH-of S-(mephenytoin) as the specific reaction was shown to be inhibited indicating that a potential interaction of topiramate with phenytoin could possibly occur in-vivo. No other isozyme appears to be involved in topiramate oxidation.

Elimination:

The major route of elimination of unchanged topiramate and metabolites in humans is via the kidneys. The mean total plasma clearance of topiramate was 29 ml/min. The mean plasma elimination half-life of topiramate was 21 hours following single and multiple dosing.

The mean renal clearance of topiramate was 14 ml/min across 100-1200 mg single oral dose range. The mean renal clearance value for the 50 and 100 mg q12h dosing regimens was 17 ml/min.

Dose Proportionality and Multiple Dose Kinetics:

In a single dose study (n = 28), as the dose was increased from 100 mg to 1200 mg, C_{max} and AUC were almost 40% and 56% higher at the 1200 mg dose compared to 100 mg dose than they should be, had there been a linear relationship between the doses.

Multiple q 12h dosing (n =19) for 50 and 100 mg doses of topiramate for at least 14 days resulted in topiramate C_{max} and AUC values that increased in a linear and dose-proportional manner.

Concomitant multiple-dose administration of topiramate 100-400 mg q12h (n =12) regimens with phenytoin and 100-600 mg q12h (n= 20) regimens with carbamazepine show dose proportional linear kinetics of topiramate. Likewise, topiramate showed dose proportionality between 100-600 mg q12h (n =3) regimens in the presence of primidone.

Between 100 to 400 mg b.i.d.(n =12) dosing, both Cmax and AUC(0-12) of topiramate were 25% less than expected (slightly non-linear) at the 400 mg b.i.d. dose in the presence of valproic acid.

Effect of Food:

There is no effect of food on the bioavailability of topiramate and therefore, topiramate can be administered without regard to food.

Renal Impairment:

This study was a single dose design in male and female subjects with renal impairment compared to subjects with normal renal function who were matched to the impaired subjects by gender, age, and weight. There were 3 males and 4 females in the group with creatinine clearance <30 ml/min/1.73m^2 and matched subjects with creatinine clearance >70 ml/min/1.73m^2. In the group of creatinine clearance 30-69 ml/min/1.73m^2, there was only one female along with 6 males and matched subjects with creatinine clearance >70 ml/min/1.73m^2.

Pharmacokinetics of topiramate in plasma and urine were affected by renal impairment, since almost 70% of the drug is excreted unchanged in urine. Oral clearance decreased by 56% in the severe group and by 46% in the moderate group as compared to normals. A four-fold decrease in the severe group and two-fold decrease in the moderate group was observed for renal clearance as compared to normals.

The group of subjects in 30-69 ml/min/1.73m^2 creatinine clearance was divided into two (i) subjects with creatinine clearance 30-50 ml/min/1.73m^2 (n = 4)
(ii) subjects with creatinine clearance 51-69 ml/min/1.73m^2 (n = 3). There was no difference in the pharmacokinetic parameters between groups of subjects whose creatinine clearance ranged either from 30-50 ml/min/1.73m^2 or 51-69 ml/min/1.73m^2.

Accumulation of topiramate would be expected to occur in epileptic patients with renal impairment if chronically dosed at the same rate as patients with normal renal function as the elimination half-life had also increased by 2 fold.

Hemodialysis: Six subjects between 25 to 43 years of age with end-stage renal disease were administered 100 mg dose of topiramate. Venous blood samples were collected just prior to topiramate administration and at selected time points upto 104 hours after dosing. Arterial blood samples were collected during the hemodialysis period at 32, 33, 34, and 35 hours after dosing. Dialysate fluid samples were collected prior to hemodialysis and for the intervals 32-33, 33-34, and 34-35 hours after dosing (total of 3 hours sampling).

Topiramate was effectively removed from the plasma by hemodialysis. Over 3 hours of hemodialysis about 19 mg of topiramate was removed from the body. The mean hemodialysis clearance of topiramate from plasma was increased approximately 11 times over the mean clearance of topiramate from plasma of the same subjects when they were not on hemodialysis.

Hepatic Impairment:

The study was a single dose study in two male and three female subjects with hepatic impairment (Child-Pugh Index 5-9) and in six healthy controls matched to the hepatically- impaired subjects by age, gender, and weight. Both C_{max} and AUC of topiramate increased by 29%, whereas its apparent clearance decreased by 29% in subjects with moderate to severe hepatic impairment. The decrease in topiramate oral plasma clearance was primarily due to decreased renal clearance (49%), although renal function appeared to be normal in these patients. There was no difference in non-renal clearance between the two groups.

Drug Interactions:

(a) In-Vitro:

In vitro studies were conducted with human liver microsomes to characterize the inhibitory spectrum of topiramate (0.5-1000 μM) using substrates and specific reactions catalyzed by specific human cytochrome P450 isoforms. These studies were done to aid in predicting potential interactions through a knowledge of the inhibitory spectrum of the drug.

Inhibition of the 4'-hydroxylation of S-mephenytoin and the 1"-hydroxylation of 1'R-bufuralol (in CYP2D6-deficient microsomes) suggests the potential for an interaction between topiramate and phenytoin in vivo.

(b) In Vivo:

Phenytoin-Topiramate Interaction:

The study was an open, escalating dose study conducted in 12 epileptic patients (7 men, 5 women). The patients were stabilized on phenytoin monotherapy (130-300 mg q12h or 360-480 mg q24h; n = 6 in each group). The topiramate dose escalation began with concomitant topiramate 100 mg qPM for 3 days, followed by 100 mg q12h for at least 11 days. Dose escalation continued by administration of topiramate 100 mg qAM and 200 mg qPM for 3 days followed by 200 mg q12h for at least 11 days. Dose escalation was completed by administration of topiramate 200 mg qAM and 400 mg qPM for 3 days followed by 400 mg q12h for at least 11 days. After two weeks of stabilization on the maximium tolerated concomitant topiramate dose, phenytoin doses were reduced by 25% at intervals of 1 week over the next 4 weeks. This was continued until patients were on topiramate or on the lowest achievable phenytoin dose. After at least 2 weeks on the final dosage regimen, topiramate doses were decreased by 200 mg at intervals of at least 1 week.

Topiramate decreased mean total and free phenytoin clearance by 20% in patients resulting in higher phenytoin plasma concentrations, however, the small sample size is small. Therefore, it is recommended that patients be regularly monitored for their clinical progress when combination therapy with topiramate is initiated.

Topiramate clearance increased by 2.5 fold during combination therapy with phenytoin, resulting in lower plasma topiramate concentrations as compared to topiramate monotherapy. Therefore, topiramate dosing regimen may require adjustment when administered with phenytoin.

Carbamazepine-topiramate Interactions:

(i) Following a 3-week baseline period of carbamazepine therapy in 12 patients (300 - 800 mg q 8h), topiramate dose escalation began with concomitant topiramate dosing of 100 mg q12h, followed by 200 mg q12h and completed by administration of topiramate 400 mg q12h. Steady state was achieved in each instance. After two weeks of stabilization on the maximium tolerated concomitant topiramate dose, carbamazepine doses were reduced by 25% at intervals of 1 week over the next 4 weeks. This was continued until patients were on topiramate monotherapy or on the lowest achievable carbamazepine dose along with topiramate. After an additional 2 weeks on the final dosage regimen of topiramate doses were decreased by 200 mg at intervals of at least 1 week.

Concomitant administration of topiramate with carbamazepine does not alter the pharmacokinetics of carbamazepine and its epoxide. Therefore, carbamazepine dosage adjustment may not be necessary when given with topiramate (topiramate dose = 100-400 mg b. i. d.).

The steady-state topiramate plasma pharmacokinetics are linear and dose proportional over the 100-400 mg b.i.d. dose range when given as adjunctive therapy to carbamazepine. Topiramate clearance with CBZ was increased by 2-fold compared to its clearance in [illegible] Therefore, to maintain equivalent topiramate concentrations during concomitant therapy with carbamazepine, the topiramate dose may need to be [illegible]

doubled. However, the clinical condition of the patients should also be monitored to optimize topiramate dose.

(ii) Six males and two females took part in this study. After 2 weeks of carbamazepine topiramate dosing was initiated with 100 mg b .i. d. The scheduled titration of topiramate dosage was increased at 1 or 2 week intervals in increment of 100 mg (every 12 hour dosing) upto tolerated dose not to exceed 600 mg b.i.d. The final pharmacokinetic profile was obtained at the end of the 8-week stabilization period at the highest tolerated dose of topiramate (CBZ dosing continued alongside). Pharmacokinetic parameters for topiramate were evaluated at steady state on 100, 300, and 600 mg b.i.d. topiramate dosing. The steady state topiramate pharmacokinetics over 100 to 600 mg b. i. d. range were linear in the presence of CBZ. The effect of topiramate on CBZ or on its metabolite CBZE was not studied.

Valproic acid-Topiramate Interaction:

The study was an open, escalating dose study conducted in 12 epileptic patients (6 men, 6 women). Topiramate and/or valproic acid were administered 1 hour before or two hours after meals . The study began with a three-week baseline period in patients with partial epilepsy who were stabilized on valproic acid (500 to 2250 mg b. i. d.). Patients continued on their established valproic acid dosing regimen during topiramate dose escalation. Topiramate dose escalation began with concomitant topiramate as 100 mg q12h. Dose escalation continued with administration of topiramate 200 mg q12h and was completed with 400 mg q12h. Steady state was achieved in each instance. After two weeks of stabilization on the maximium tolerated concomitant topiramate dose, valproic acid doses were reduced by 25% at intervals of 1 week over the next 4 weeks. This was continued until patients were on topiramate or on the lowest achievable valproic acid dose. After an additional 2 weeks on the final dosage regimen of topiramate, its doses were to be decreased by 200 mg at intervals of at least 1 week

The results of this study indicate that VPA increases the clearance of topiramate by 15% when the highest dose of topiramate was administered (400 mg b.i.d.). In turn, the 400 mg b.i.d. dose of topiramate showed a 13% increase in the clearance of VPA; this was the maximum change observed for VPA across the topiramate doses.

Phenytoin-Topiramate or Valproic Acid-topiramate Interaction:

Following a 2-week baseline period of either phenytoin 200-730 mg/day (n = 5) or valproic acid 1000-3500 mg/day (n = 4) and while continuing on their established anticonvulsant dosing regimen, patients were started on topiramate 100 mg b. i. d. for 2 weeks. The topiramate dose was titrated up to its maximum tolerated dose, not to exceed 600 mg b.i.d. Doses were titrated in increments of 100 mg over an 8-week period. Patients were then maintained at the maximum tolerated topiramate dose for an additional 8 weeks (stabilization period). Topiramate pharmacokinetic parameters were assessed at the 100 and 300 mg b.i.d. doses only, since the number of patients with data at other topiramate doses was limited to one patient on each dose.

Topiramate exhibited dose proportional pharmacokinetics when given along with phenytoin or valproic acid. The $AUC_{(0-12)}$, C_{max}, $C_{min(0)}$, and $C_{min(12)}$ were lower by approximately 2.5, 2, 3, and 3 folds, respectively in group of patients who received concomitant phenytoin than in patients receiving concomitant valproic acid. Oral clearance was about 2.4 fold higher in patients receiving phenytoin than valproic acid, though renal clearance was unchanged in both the groups. The percent of topiramate dose excreted in urine was almost two fold higher in the group of patients who received concomitant valproic acid than the group receiving phenytoin. This suggests that there is an increase in the metabolic clearance of topiramate in the presence of phenytoin.

The study does not provide information on the effect of topiramate on either phenytoin or valproic acid.

Primidone-Topiramate Interaction:

This was an open, ascending dose study in 3 patients. Patients were already on a 2-week baseline of primidone, when topiramate dosing began as 100 mg b .i. d. for two weeks. Titration of topiramate increased at 2-week intervals in increments of 100 mg not to exceed 600 mg b.i.d. Pharmacokinetics were evaluated following topiramate administration of 100, 300, and 600 mg b.i.d.

AUC (0-12 h) appears to be proportional between 100 to 600 mg b.i.d. topiramate dose in the presence of primidone. Oral clearance does not change across doses. This study does not mention the effect of topiramate on the pharmacokinetics of primidone due to inconsistent trough levels seen for primidone.

Phenobarbital-Topiramate Interaction:

Patients involved in a drug-interaction study for phenobarbital dropped out and the study could not be completed. Population pharmacokinetic analysis (data obtained from Phase II clinical studies) indicated that there is no affect of phenobarbital on topiramate.

Digoxin-Topiramate interaction:

This was an open, sequential, two-period, two-treatment study in which the effect of pretreatment with a 100 mg b.i.d. oral regimen of topiramate for 6 days was studied on the pharmacokinetics of a 0.6 mg single oral dose of digoxin in 12 healthy male subjects.

Both C_{max} and AUC (0-inf) of digoxin decreased by 16% and 12%, respectively in the presence of topiramate. Pretreatment of digoxin with topiramate did not affect t_{max} or $t_{1/2}$ of digoxin. Oral clearance of digoxin increased by 13% in the presence of topiramate. Digoxin was given to healthy volunteers as a single oral dose, but the results could be more pronounced if digoxin were dosed to steady state. The study does not provide information on the effect of digoxin on the pharmacokinetics of topiramate.

Pharmacokinetic and Pharmacodynamic Relationships:

These studies were multicenter, outpatient, parallel, double-blind, randomized, placebo-controlled, adjunctive therapy clinical studies to compare the safety and efficacy of different topiramate doses in patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs. Following a baseline period, patients were randomly assigned to placebo or to a topiramate dose. Dose groups ranged from 200 to 1000 mg per day. Topiramate doses were titrated up to the assigned dose or to the maximum tolerated dose. Trough plasma samples (8-16 hrs postdose) were collected throughout the titration and stabilization periods of the study. Percent reduction in seizure rate was defined as:

$$\text{Seizure rate} = 100\ (B-S)/B$$

Where B = baseline seizure rate and S= stabilization period seizure rate.

There was a decrease from baseline seizure rate due to topiramate therapy, however, there was no correlation between percent reduction in seizure rate and steady-state plasma topiramate concentration. The median percent reduction in seizure rate was seen to increase with increasing plasma topiramate concentrations up to 5.2 µg/mL. At plasma topiramate concentrations above 5.2 µg/mL, a decrease from the peak seizure rate reduction was observed.

Population Analysis for Age, Gender and Race:

Three phase II studies (multicenter, outpatient, parallel, and randomized) were designed to evaluate the safety and efficacy of 200, 400, 600, 800, and 1000 mg daily doses of topiramate in two equally-divided doses compared with placebo as adjunctive therapy for 427 patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs. Topiramate dose was titrated up to the assigned dose or to the maximum tolerated dose (increments were usually weekly).

The addition of weight on clearance did not reduce the objective function significantly (2045 for no weight effect vs 2044.5 for weight effect). The addition of

weight on both clearance and volume produced a significant reduction in the objective function (2045.6 for no weight effect vs 2037.9 for weight effect). Based upon this reduction of objective function, a model for both clearance and volume with weight as a covariate was selected. Further analysis indicated that there was no affect of age, gender, or race on topiramate clearance. Race and gender appeared to affect topiramate volume, but not age.

Protein binding:

In-vitro protein binding study using equilibrium dialysis indicated that topiramate is 17% bound to plasma proteins over the concentration range of 1-250 µg/mL (the clinically relevant plasma concentration of topiramate was as high as 33 µg/mL).

Formulation Links:

The Sponsor has established linkage between Phase II and Phase III tablet formulations (100 mg and 400 mg tablets). The Phase III tablet formulations were the same for pharmacokinetic and clinical studies and will also be the marketed formulation. The Sponsor will market 100, 200

However, the Sponsor is requesting for bioavailability waiver for the 200 and tablets claiming that both active and inactive ingredients of 200 and tablets This request can be accommodated based on linear kinetics of drug, compositional proportionality of the three strengths and the rapid dissolution profiles.

Dissolution:

TOPIRAMATE LABELING

Absorption:

Absorption of topiramate is rapid with peak plasma concentration of 27 μg/ml occurring at approximately 2 hours following 400 mg oral doses every 12 hours. The bioavailability of tablet relative to solution is approximately 82%. Bioavailability of topiramate is not affected by food.

Distribution:

The volume of distribution (V/F) of topiramate following 100 to 1200 mg oral doses ranged from 0.55 l/kg to 0.8 l/kg. Topiramate is 17% bound to human plasma proteins over the concentration range of 1-250 μg/mL.

Metabolism:

A total of 81.3 ± 4.3% of the administered dose was recovered in excreta in a 10-day period. In urine 80.6 ± 4.3% of the dose was excreted as total radioactivity, whereas only 0.72 ± 0.3% of the dose was excreted in feces. Unchanged topiramate accounted for 70% of the radioactivity in urine.

Unchanged topiramate plus six trace metabolites (each <5% of the sample) were characterized from the plasma, urine, and feces in humans. The pathways for the formation of these metabolites are hydroxylation, hydrolysis and glucuronidation.

Elimination:

Topiramate and its metabolites are excreted via the kidneys. The mean total plasma clearance of topiramate was 29 ml/min with plasma elimination half-life of 21 hours. The mean renal clearance for the 50 and 100 mg q12h dosing regimens was 17 ml/min.

Dose Proportionality and Multiple Dose Kinetics:

Topiramate exhibited linear kinetics over the dose range of 50 to 100 mg given every 12 hours. In epileptic patients who were maintained on either phenytoin, carbamazepine or primidone, topiramate showed linear kinetics over the dose range of 100-600 mg q 12hr. However, in the presence of valproic acid topiramate levels were 23% lower than linearly expected.

Special Populations:

Renal Impairment:

Accumulation of topiramate would be expected to occur in epileptic patients with renal impairment if chronically dosed at the same regimen as patients with normal renal function. The oral clearance of topiramate was reduced in moderately (creatinine clearance 30-69 ml/min/1.73m^2; 6M, 1F) and severely renally impaired subjects (creatinine clearance <30 ml/min/1.73m^2; 3M, 4F) by 46% and 56%, respectively as compared to matched normal renal function subjects (creatinine clearance >70 ml/min/1.73m^2). A four-fold decrease in the severe group and a two-fold decrease in the moderate group was observed for renal clearance as compared to normals.

Hemodialysis:

Topiramate was effectively removed from the plasma by hemodialysis. Over 3 hours of hemodialysis about 19 mg of topiramate was removed from the body. The mean hemodialysis clearance of topiramate from plasma was increased approximately 11 times over the mean clearance of topiramate from plasma of the same subjects when they were not on hemodialysis.

Hepatic Impairment:

In hepatically impaired subjects (2M, 3F), the oral clearance of topiramate was decreased by 29% as compared to those with normal hepatic function.

Age, Gender and Race:

Clearance of topiramate was not affected by age, gender or race.

Pharmacodynamics:

In three multicenter clinical studies designed to compare the safety and efficacy of different doses of topiramate (200-1000 mg/day) in patients with refractory partial epilepsy, the median percent reduction in seizure rate was seen to increase with increasing plasma topiramate concentrations up to 5.2 µg/mL. At plasma topiramate concentrations above 5.2 µg/mL a decrease from the peak seizure rate reduction was observed.

PRECAUTIONS:

Drug Interactions:

In-Vivo:

The drug interaction data described in this section were obtained from controlled clinical trials and studies involving healthy adults and patients with epilepsy. The results of these interactions are summarized in the following table:

AED Co-administered	AED Concentration	TOPAMAX™ Concentration
Phenytoin	Increased	decreased
CBZ	No change	decreased
CBZ-epoxide*	No change	
Valproic acid	Decreased	decreased
Phenobarbital	-	No change

* = Is not administered but is an active metabolite of carbamazepine

AED = Antiepileptic drug

Effects of Topiramate on the pharmacokinetics of other antiepileptic drugs:

Topiramate added to phenytoin: Topiramate decreases free and total phenytoin clearance by 20% in patients resulting in higher phenytoin plasma concentrations.

Topiramate added to carbamazepine: Concomitant administration of topiramate with carbamazepine does not alter the pharmacokinetics of carbamazepine and its epoxide.

Topiramate added to valproic acid: Topiramate showed a 13% increase in the clearance of VPA.

Effects of other antiepileptic drugs on the pharmacokinetics of Topiramate:

Phenytoin added to topiramate: Topiramate clearance increased by 2.5 fold during combination therapy with phenytoin, resulting in lower plasma topiramate concentrations as compared to topiramate monotherapy.

Carbamazepine added to topiramate: Topiramate clearance was increased by 2-fold in the presence of carbamazepine as compared to its clearance in monotherapy.

Valproic acid added to topiramate: Valproic acid increases the clearance of topiramate by 15%.

Phenytoin-Topiramate or Valproic Acid-Topiramate Interaction: Oral clearance of topiramate was about 2.4 fold higher in patients receiving phenytoin than those receiving valproic acid, though renal clearance was unchanged in both the groups. The percent of topiramate dose excreted in urine was almost two fold higher in the group of patients who received concomitant valproic acid than the group receiving phenytoin. This may suggest that there is an increase in the metabolic clearance of topiramate in the presence of phenytoin.

Digoxin-topiramate interaction:

A single dose of digoxin increased its clearance by 13% in the presence of steady state topiramate.

Renal:

In renally impaired patients (creatinine clearance < 70 ml/min/1.73m^2) and patients on hemodialysis, topiramate should be administered with caution (see also Dosage and Administration).

Hepatic:

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate was decreased as compared to normal subjects.

Dosage and Administration:

Renal:

In renally impaired subjects with creatinine clearance less than 70 ml/min/1.73m^2, one half of the normal adult dose is recommended.

Drug Interactions:

Topiramate:

Based on the observed increase in clearance of topiramate by 2-2.5 fold upon concomitant administration with phenytoin or carbamazepine, a higher dose of topiramate may be required.

Phenytoin:

Caution should be exercised when topiramate and phenytoin are administered concomitantly, since free and total phenytoin clearance decreased by 20%.

Biopharm Day: October 3, 1995

Iftekhar Mahmood, Ph.D. Imahmood 10/4/95

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 10/5/95

Pharmacokinetics Evaluation Branch I

CC: NDA 20-505, HFD-120, HFD-426 (Mahmood, Baweja, Fleischer), HFD-427 (Chen Me), HFD-340 (Viswanathan), Chron, Drug, Reviewer and FOI (HFD-19) files.

Bioavailability And Pharmacokinetic Studies Of Topiramate

Study #1: Comparative bioavailability of topiramate from two 100 mg tablet formulations (formula #1 and 37) administered in the fasted state to healthy male subjects (MS 212, April 1993).

The objective of this single dose study was to compare the 100 mg market image tablets (formula #37, Batch # R4539, manufactured at McNeil Pharmaceuticals, Dorado, Puerto Rico, Date of Mfg: July, 1991) and 100 mg tablets used in clinical trials (formula #1, Batch # R4504, manufactured at McNeil Pharmaceuticals, Spring House, PA, Date of Mfg: Febraury, 1991). The clinical trial was conducted from October 12, 1991 to November 9, 1991.

The study was a randomized, complete, two-way crossover. Eighteen healthy male subjects who took part in this study (age ranging from 20 to 31 years, weight ranging from 153 to 190 lbs), received a 100 mg oral dose of topiramate as one tablet on each dosing day, separated by a three-week washout period. Seven ml venous blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 84, 96, 120, 144, and 168 hours. Plasma samples were analyzed for topiramate by validated capillary gas chromatography with nitrogen phosphorus detection. Using 500 µl plasma, the limit of detection was 0.1 µg/mL.

Results:

The pharmacokinetic parameters C_{max}, T_{max}, AUC (0-infinity), oral clearance (CL/F), and half-life of topiramate from the two treatments are summarized in the following table .

PK parameters	Treatment A (Formula #1) (Clinical reference)	Treatment B (Formula #37) (Test)
$T_{1/2}$ (hrs)	39.1 ± 11.7	39.0 ± 8.1
C_{max} (µg/ml)	1.5 ± 0.3	1.5 ± 3.1
T_{max} (hrs)	2.9 ± 2.6	2.9 ± 2.6
$AUC_{(0\text{-inf})}$ (µg.h/ml)	58.6 ± 9.5	59.5 ± 10.4
CL/F (ml/min)	29.2 ± 5.0	28.9 ± 5.8

Mean ± SD

Statistical comparisons of AUC and Cmax by ANOVA indicated that there were no significant differences between the two treatments. The two, one-sided tests procedure showed that the 90% confidence intervals for AUC and C_{max} of the market image tablet (B) were within ± 20% of the mean values for treatment A. T_{max} for both treatments was comparable (2.9 hrs). Therefore, it can be concluded that the market image tablet is bioequivalent to the tablet used in the clinical trials. The following table summarizes the market vs clinical bioequivalence study of topiramate 100 mg tablet.

90% Confidence Interval for the ratio of the two treatment means on log scale

	90% Confidence Interval	
Parameter	Lower limit (%)	Upper limit (%)
AUC (0-t)	96.8	107.5
AUC (0-inf)	96.2	106.8
C_{max}	89.9	104.6

Ratio = mean for market/mean for clinical

Conclusions:

The market image 100 mg tablet is bioequivalent to the 100 mg tablet used in the clinical trials.

Study #2: Comparative bioavailability of topiramate from a 100 mg tablet formulation (formula #1) a 400 mg tablet formulation (formula #36) administered as a 400 mg dose in the fasted state to healthy male subjects (MS 213, April 1993).

The objective of this study was to compare the bioavailability of topiramate between the 100 mg tablet (formula #1,Batch # R4504, manufactured at McNeil Pharmaceuticals, Spring House, PA) used in clinical trials and the 400 mg tablet (formula #36, Batch # R4541, manufactured at McNeil Pharmaceuticals, Dorado, Puerto Rico, Date of Mfg: July, 1991) administered at an equal 400 mg dosage to healthy male subjects under fasted conditions.

The study was a randomized, complete, two-way crossover. Eighteen healthy male subjects took part in this study in a crossover fashion separated by a three-week washout period between treatments.

Treatment A: A single oral 400 mg dose as four 100 mg tablets of clinical trial (formula #1) with 240 ml of water following a 10-h overnight fast.

Treatment B: A single oral 400 mg dose as one 400 mg tablet of market image (formula #36) with 240 ml of water following a 10-h overnight fast.

Ten ml blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 84, 96, 120, 144, and 168 hours. Plasma samples were analyzed for topiramate by validated capillary gas-liquid chromatography with nitrogen phosphorus detection. The limit of detection was 0.5 µg/mL.

Results:

The pharmacokinetic parameters C_{max}, T_{max}, AUC (0-infinity), oral clearance (CL/F), and half-life of topiramate from the two treatments are summarized in the following table.

PK parameters	Treatment A (Formula #1) (4 X 100 mg tablets) (Clinical reference)	Treatment B (Formula #36) (1 X 400 mg tablets) (Test)
$AUC_{(0-t)}$ (µg.h/ml)	276.5 ± 38.8	268.4 ± 62.3
$AUC_{(0-inf)}$ (µg.h/ml)	302.1 ± 42.5	293.0 ± 64.9
C_{max} (µg/ml)	8.2 ± 1.3	7.8 ± 1.4
T_{max} (hrs)	2.0 ± 1.7	2.3 ± 1.4
CL/F (ml/min)	24.0 ± 3.5	26.4 ± 10.8
$T_{1/2}$ (hrs)	27.2 ± 4.3	28.1 ± 5.3

Statistical comparisons of AUC and Cmax by ANOVA indicated that there were no significant differences between the two treatments. The two, one-sided tests procedure showed that the 90% confidence interval for AUC and Cmax of the market image tablet were within ± 20% of the mean values for treatment A. T_{max} for both treatments was comparable (approximately 2 hrs). Therefore, it can be concluded that 1 X 400 mg market image tablet is bioequivalent to 4 X 100 mg tablets used in the clinical trials. The following table summarizes the market vs clinical bioequivalence study of topiramate.

90% Confidence Interval for the ratio of the two treatment means on log scale

		90% Confidence Interval
Parameter	Lower limit (%)	Upper limit (%)
AUC (0-t)	85.7	104.6
AUC (0-inf)	87.1	103.7
C_{max}	84.6	103.1

Ratio = mean for market/mean for clinical

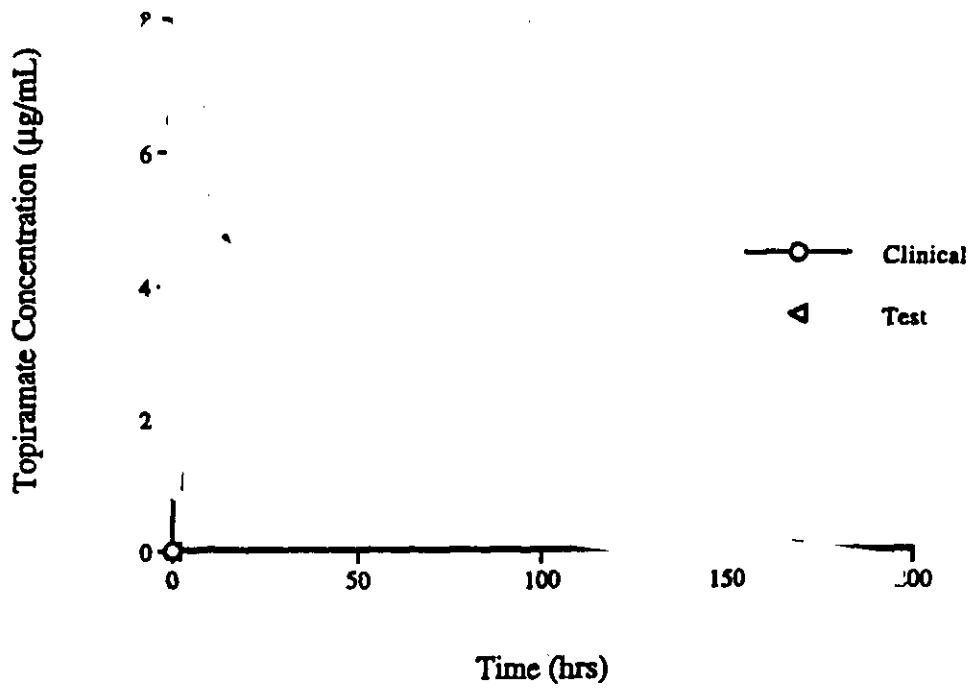
Conclusion:

One 400 mg market image tablet is bioequivalent to 4 X 100 mg clinical trial tablets.

Comments:

Topiramate concentrations can be measured as low as 0.1 µg/mL, but in this study the limit of detection was 0.5 µg/mL. This could have affected the extrapolation of AUC from time 't' to infinity. Though only 10% of the extrapolated area has contributed to total AUC (0-infinity) in this particular study, there is always a possibility that by stopping sampling at much higher quantitation limit, a higher percentage of tail will be added to the total area.

Mean Plasma Topiramate Concentrations vs Time



Study # 3: Evaluation of the Relative Bioavailability of Topiramate from a 100 mg Tablet (Formula #1) with Reference to a Solution Dosage Form and the Effect of Food on the Bioavailability of Topiramate from the Tablet Dosage form (MS-174, September 1993).

OBJECTIVES:

The objectives of this study were to determine the bioavailability of a 100 mg oral tablet (Formula #1, clinically studied) of topiramate administered in the fasted state relative to 100 mg of topiramate administered as an oral, aqueous solution in the fasted state, and to determine the oral bioavailability of the 100 mg tablet of topiramate administered in the fed state relative to the 100 mg tablet administered in the fasted state.

FORMULATION:

100 mg Tablet Batch No. R4314, Formula No. 1, manufactured at Spring House, PA.
Date of Mfg: August, 1987.
100 mg Powder Batch No. R4313, manufactured at Spring House, PA.
The clinical trial was conducted in November 1987.

STUDY DESIGN AND SAMPLING:

The study was an open, randomized three-way crossover in 21 healthy male subjects. Each subject received all three 100 mg oral doses of topiramate separated by 7-day washout periods. The treatments were as follows:
Treatment A = 100 mg tablet, fasted
Treatment B = 100 mg tablet, fed
Treatment C = 100 mg solution, fasted.

One subject was excluded from the study because the treatments were administered out of assigned order. The subjects' age ranged from 21 to 45 years and body weight was from 144 to 192 pounds. Serial blood samples were collected upto 96 hours and urine

RESULTS:

Significant concentrations of topiramate were found in the predose plasma and urine samples from the second and the third treatment. Due to this carryover, standard

statistical analysis of the data from all three treatment periods was not possible, therefore, statistical analysis was only done from the first dosing period of this study. Data from 5 subjects (Treatment A), 6 subjects (Treatment B), 6 subjects (Treatment C) were analyzed by ANOVA according to a single dose, 3 parallel group treatment study design.

The statistical analysis showed that there is no difference between all three treatments for AUC, CL/F and $t_{1/2}$, but C_{max} was an exception. However, the power of ANOVA to detect at 20% difference from the reference mean from these parameters was not sufficient to conclude bioequivalence. The two, one-sided test results showed that the 90% confidence intervals for the difference in means exceeded the 80%-125% limits required for demonstration of bioequivalence in all comparisons.

Pharmacokinetic Parameters (Mean ± SD) of Topiramate in Plasma and Urine

Parameter	100 mg Tablet Fasted (N=5)	100 mg Tablet Fed (N=6)	100 mg Solution Fasted (N=6)
C_{max} (µg/mL)	1.95 ± 0.21	1.63 ± 0.15	2.27 ± 0.61
T_{max} (h)	1.30 ± 0.97	4.17 ± 2.04	2.58 ± 2.80
AUC (0-t) (µg*h/mL)	50.75 ± 7.67	53.80 ± 9.41	61.72 ± 10.3
AUC (0-∞)(µg*h/mL)	59.15 ± 9.02	62.09 ± 12.7	71.57 ± 11.2
t1/2 (h)	26.92 ± 4.66	33.02 ± 4.28	34.86 ± 14.9
Ur Excr (0-72 h) mg	43.71± 5.48	37.02 ± 4.04	40.51± 6.22
CL/F (mL/min)	28.74 ± 4.63	27.83 ± 5.81	23.77 ±3.73
CL_R (mL/min)	14.73 ± 3.63	12.99 ± 2.30	12.21± 2.31

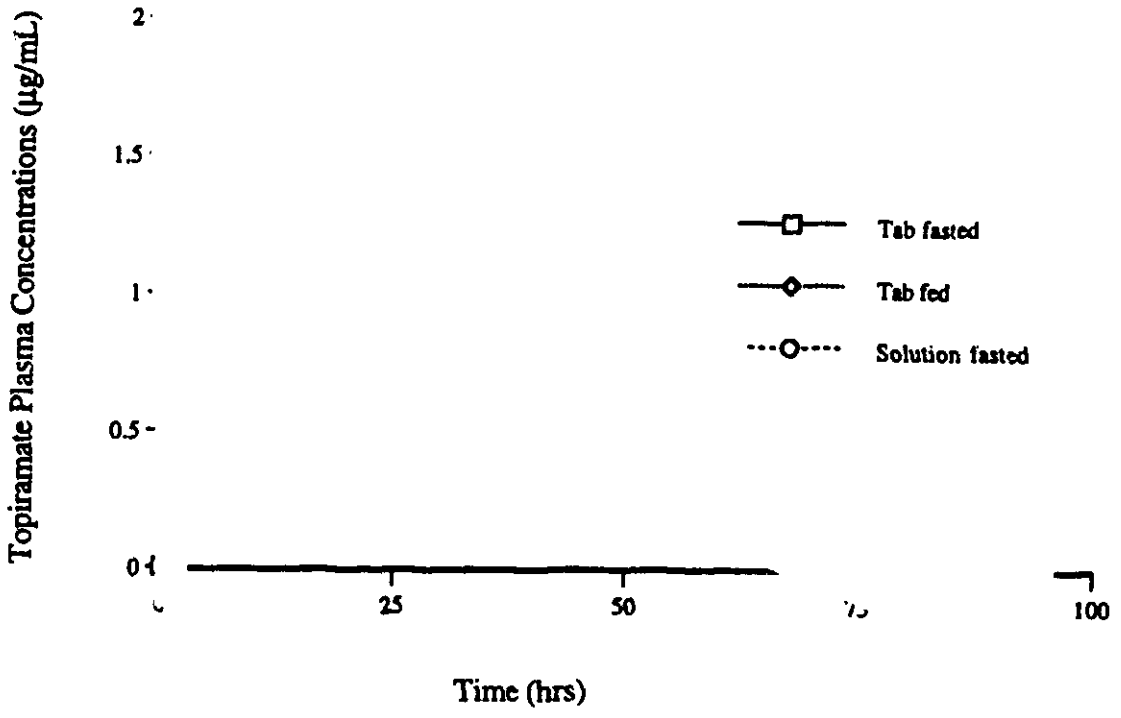
CONCLUSIONS:

Due to incomplete wash-out between dosing periods, evaluation of relative bioavailability was restricted to data from the first dosing period. Comparison across parallel treatment groups indicated that the relative bioavailability of topiramate from the tablet was approximately 82% with reference to the solution. The effect of food on the bioavailability of clinical tablet was minimal; mean t_{max} was delayed by food by approximately 3 hours. The mean pharmacokinetic parameters are summarized in Table 5 above. The data are from treatment period 1 only.

Comments:

The earlier two bioequivalence studies had a 3-week washout period between treatments. This study had a 7-day washout, which appeared inadequate, and therefore periods 2 and 3 showed plasma levels for pre-dose.

Topiramate Mean Plasma concentrations following fed and fasted conditions



Study #4: Effect of Food on the Bioavailability of Topiramate from Oral Administration of One 100 mg Tablet (Formula # 37) of Topiramate in Healthy Male Subjects (MS-211, September, 1992).

OBJECTIVES:

The objective of this study was to determine the effect of food on the bioavailability of topiramate following administration of a 100 mg market image tablet to healthy male subjects.

FORMULATION:

100 mg Tablet Batch No. R4539, Formula # 37, manufactured at Dorado, Puerto Rico. The study was conducted from October 13, 1991 to November 10, 1991.

STUDY DESIGN AND SAMPLING:

The study was a randomized, complete, two-way crossover study in which 18 healthy male subjects received both treatments (100 mg tablet administered in the fasted condition, and 100 mg tablet administered in the fed condition), one on each of two different dosing days. One subject was excluded from the study due to protocol violation. The dosing days were separated by a washout period of 3 weeks. Blood samples were collected for 168 hours (7 days) following each treatment. Topiramate concentration was measured in plasma till 60 hrs using a sensitive and specific capillary gas chromatography. The sensitivity of the assay was 0.5 μg/mL.

RESULTS:

The statistical analysis showed that there is no difference between the two treatments for AUC, CL/F and $t_{1/2}$ and C_{max}. Tmax was delayed by food by about 1.6 hrs. The two, one sided tests for bioequivalence showed that the 90% confidence intervals for AUC and Cmax were within ± 20% of the mean for the fed and the fasted treatment. The mean pharmacokinetic parameters are summarized in the table below. Data on 90% CI can be found in Appendix 2.

Pharmacokinetic Parameters (Mean ± SD) of Topiramate in Plasma

Parameter	100 mg Tablet Fasted	100 mg Tablet Fed
C_{max} (µg/mL)	1.63 ± 0.26	1.46 ± 0.13
T_{max} (h)	1.4 ± 1.0	3.0 ± 1.6
AUC (0-t) (µg*h/mL)	34.2 ± 7.2	34.1 ± 7.4
$AUC_{(0-\infty)}$ (µg*h/mL)	59.8 ± 8.6	57.3 ± 9.1
t1/2 (h)	30.4 ± 5.3	28.2 ± 2.6
CL/F (mL/min)	28.5 ± 4.4	29.8 ± 4.7

CONCLUSIONS:

The effect of food on the bioavailability of a 100 mg market-image tablet formulation may not be clinically significant. Though food is causing an almost 1.5 hour delay for t_{max}, and there is an 11% decrease in C_{max} and a 4% decrease in AUC, this may not be clinically relevant.

Comments:

Due to the stoppage of sampling at quantitation limit of 0.5 µg/mL, the tail of plasma conc vs time has contributed almost 73% of the total area.

Study #5: Effect of Food on the Bioavailability of Topiramate from Oral Administration of One 400 mg Tablet (Formula # 36) of Topiramate in Healthy Male Subjects (MS-214, Nov 1992).

OBJECTIVES:

The objective of this study was to determine the effect of food on the bioavailability of topiramate following oral administration of a 400 mg tablet of topiramate to healthy male subjects.

FORMULATION:

400 mg Tablet Batch No. R4541, Formula No. 36, manufactured at Dorado, Puerto Rico (market image).

STUDY DESIGN AND SAMPLING:

The study was a randomized, complete, two-way crossover study in which 18 healthy male subjects received the two treatments, (a 400 mg tablet in the fasted condition and a 400 mg tablet in the fed condition) on each of two dosing days. Subjects who were dosed in the fed state received a standard breakfast (no mention of food content) within 15 minutes prior to dosing. The dosing days were separated by a washout period of 3 weeks. Blood samples were collected for 168 hours (7 days) following each dose. Topiramate concentration was measured in plasma using a sensitive and specific capillary gas chromatography. The sensitivity of the assay was 0.5 μg/mL.

RESULTS:

The statistical analysis showed that there is no difference between the two treatments for AUC, CL/F and $t_{1/2}$ but C_{max} was an exception. The extent of absorption of topiramate from the fed state was 12.6% greater than from the fasted state. The C_{max} was statistically different within the treatment groups, but 90% confidence interval showed that the mean for the test was within ± 20% of the mean of the reference. The mean pharmacokinetic parameters are summarized in the table below.

Pharmacokinetic Parameters of Topiramate in Plasma

Parameter	400 mg Tablet Fasted	400 mg Tablet Fed
C_{max} (µg/mL)	8.00 ± 1.00	6.98 ± 0.92
T_{max} (h)	2.7 ± 1.9	4.8 ± 2.4
AUC (0-∞) (µg*h/mL)	311.2 ± 118.2	350.3 ± 197.9
AUC (0-t) (µg*h/mL)	276.0 ± 99.6	306.0 ± 149.7
t1/2 (h)	28.9 ± 3.9	31.3 ± 10.2
CL/F (mL/min)	23.0 ± 4.8	22.0 ± 6.0

Mean ± SD

CONCLUSIONS:

A 13% decrease in C_{max}, a 13% increase in AUC and a 2-hr delay in t_{max} of topiramate was noted. Although T_{max} was prolonged by two hours in the fed state, the trend was not the same with all subjects (there were subjects whose T_{max} was lower in the fed states than fasted), therefore the prologation of T_{max} in fed state may be an artifact. The effect of food on the bioavailability of a 400 mg market-image tablet formulation may not be clinically significant.

Study # 6. An Ascending, Multiple Dose Safety Study of Topiramate in Healthy Men: Pharmacokinetics, Safety and Tolerability (Protocol YB/CSS-81, Dec 1994).

OBJECTIVES:

The objective of this study was to assess the safety, acceptability and pharmacokinetics of single and multiple oral doses of topiramate.

Formulation:

The drugs were provided by McNeil Pharmaceuticals as identically appearaing matched tablets containing 50 mg of topiramate (Formula #2, Batch # R4239) or placebo, or matched tablets containing 100 mg topiramate (Formula #1, Batch # R4226) or placebo. Both tablet formulations were manufactured at McNeil Pharmaceutical Co., Spring House, PA.

STUDY DESIGN AND SAMPLING:

The study was a double-blind, placebo-controlled, parallel group, ascending dose study. Subjects were divided into three dose level groups of 14 subjects each. Within each group, ten subjects were randomly assigned to receive topiramate and four the placebo according to the following dosing schedule:

Group 1	Day 1	50 mg topiramate (or placebo), single dose
	Days 3-16	50 mg topiramate (or placebo), once daily (q 24h)
	Days 17-30	50 mg topiramate (or placebo), twice daily (q 12h)
	Day 31	50 mg topiramate (or placebo), single dose
Group 2	Day 1	100 mg topiramate (or placebo), single dose
	Days 3-16	100 mg topiramate (or placebo), once daily (q 24h)
	Days 17-30	100 mg topiramate (or placebo), twice daily (q 12h)
	Day 31	100 mg topiramate (or placebo), single dose
Group 3	Day 1	200 mg topiramate (or placebo), single dose
	Days 3-23	200 mg topiramate (or placebo), once daily (q 24h)

Blood samples were collected after days 1 (up to 48 hours), 16 (up to 24 hours), 23 (up to 168 hours for the 200 mg group only), and 31 (up to 48 hours for the 50 and 100 mg groups only). Urine samples were collected after dosing on days 1 (up to 48 hours), 16 (up to 24 hours), 23 (up to 24 hours for the 200 mg group only), and 31 (up to

24 hours for the 50 and 100 mg groups only). Predose plasma samples were obtained on days 14 and 29 (50 and 100 mg groups only) to test for the attainment of steady state. Concentrations of topiramate were measured in plasma, and urine by a capillary gas chromatographic assay with nitrogen phosphorous detection. The sensitivity of the assay was as follows·

Plasma: 0.1 μg/mL (for 50 mg dose), 0.5 μg/mL (for 100 and 200 mg dose) and 1.0 μg/mL and 5.0 μg/mL for urine assays.

RESULTS:

Single Dose: The absorption of topiramate was rapid with t_{max} reaching between 2-3 hours. Intrasubject variability for C_{max} and AUC was between 15 to 30%. Single dose plasma topiramate C_{max}, AUC and cumulative amount excreted in urine increased in greater than proportional manner over the dose range of 50-200 mg. This nonlinearity was evident from a decrease in oral clearance at higher doses. This greater than proportional increase in C_{max} and AUC may be due to the concentration dependent binding of topiramate to erythrocytes. At concentrations (< 4 μg/mL) topiramate is bound to erythrocytes, whereas saturation of this binding occurs at concentration above 4 μg/mL. In single dose study, there is a big difference between AUC 0-16 hours and 0-infinity. The extrapolation has caused an addition of 230%, 177% and 169% on the mean AUCs of 50, 100 and 200 mg dose of topiramate, respectively. This large extrapolation may not indicate true clearance of topiramate.

The mean pharmacokinetic parameters following a single 50, 100 and 200 mg dose of topiramate are summarized in the following tables.

Plasma and urine pharmacokinetic parameters following single dose of Topiramate

Parameter	50 mg Dose (n =10)	100 mg Dose (n =10)	200 mg Dose (n =10)
C_{max} (µg/mL)	0.52 ± 0.12	1.34 ± 0.23	3.56 ± 1.02
T_{max} (h)	3.1 ± 2.3	2.5 ± 2.4	2.9 ± 1.3
AUC (0-16 h) (µg*h/mL)	5.2 ± 1.3	15.2 ± 1.4	35.4 ± 6.7
AUC (0-∞) (µg*h/mL)	17.2 ± 3.0	42.1 ± 9.8	95.1 ± 19.6
t1/2 (h)	27.0 ± 7.4	24.7 ± 9.4	25.6 ± 6.3
Ur.Exc (% Dose) [0-48 h]	29.73 ± 4.00	35.37 ± 7.32	38.69 ± 6.07
CL/F (mL/min)	49.9 ± 9.0	41.2 ± 7.8	36.4 ± 7.4
CL_R (mL/min)	23.8 ± 9.6	22.4 ± 4.4	18.9 ± 4.4

Mean ± SD

However, topiramate will be administered chronically and therefore a single-dose pharmacokinetic study will not be of much clinical value.

Multiple Dose: Twice daily dosing of topiramate for 14 days showed a dose proportional increase in C_{max} and AUC. The multiple dose study indicated that oral clearance was comparable within the dose range of 50-100 mg q 12hrs. Once daily dosing of topiramate for 14 days resulted a linear increase with dose and both AUC and oral clearance were independent of dose.

The mean pharmacokinetic parameters following multiple dosing of 50, 100 and 200 mg topiramate are summarized in the tables below.

Plasma and Urine Pharmacokinetic Parameters for Topiramate after q 12h dosing

Parameter	50 mg Dose (n = 9) q12h Day 31	100 mg Dose (n = 10) q12h Day 31
C_{max} (µg/mL)	3.61± 0.68	6.76 ± 2.81
T_{max} (h)	1.9 ± 0.9	3.0 ± 2.0
AUC (0-12 h) (µg*h/mL)	31.6 ± 6.6	57.2 ± 15.8
t1/2 (h)	21.8 ± 3.6	20.6 ± 2.4
C_{min} (ss) [0 h] (µg/mL)	2.01 ± 0.40	3.45 ± 1.27
C_{min} (ss) [12 h] (µg/mL)	2.35 ± 0.59	3.67 ± 1.33
CL/F (mL/min)	27.5 ± 6.4	31.0 ± 7.9
Urinary Excretion % Dose [0-12 h]	63.7 ± 12.0	52.3 ± 9.0
CL_R (mL/min)	17.8 ± 6.6	16.7 ± 6.5

Plasma and Urine pharmacokinetic Parameters following multiple dosing of topiramate q 24h dosing

Parameter	50 mg q24h Day 16 (n = 9)	100 mg q24h Day 16 (n = 10)	200 mg q24h Day 16 (n = 9)	200 mg q24h Day 23 (n = 7)
Cmax (µg/mL)	2.23 ± 0.44	3.75 ± 0.55	7.47 ± 0.97	7.64 ± 1.65
Tmax (h)	2.7 ± 2.2	2.7 ± 1.8	2.7 ± 2.1	2.6 ± 2.5
AUC (0-24 h) (µg*h/mL)	29.6 ± 3.5	56.2 ± 10.9	107.4 ±17.4	115.8 ± 26.7
t1/2 (h)	20.8 ± 7.6	21.0 ± 4.6	19.8 ± 6.8	21.2 ± 1.8
Cmin (ss) [0 h] (µg/mL)	0.85 ± 0.18	1.61 ± 0.45	3.02 ± 0.88	3.67 ± 0.59
Cmin (ss) [24 h] (µg/mL)	0.80 ± 0.17	1.63 ± 0.36	3.08 ± 1.15	2.87 ± 0.90
CL/F (mL/min)	28.5 ± 3.4	30.8 ± 7.0	31.6 ± 4.1	30.0 ± 6.3
Urin Exc % Dose [0-24 h]	67.0 ± 8.3	57.0 ± 12.2	55.9 ± 6.0	49.6 ± 6.8
CLR (mL/min)	19.1 ± 2.9	18.1 ± 7.1	17.5 ± 3.2	14.9 ± 5.0

Mean ± SD

CONCLUSIONS:

Absorption of topiramate was rapid and the intersubject variability in the pharmacokinetics parameters was low. Multiple dose plasma C_{max} and AUC increased in proportion with dose (linear pharmacokinetics) following 12 and 24 hr dosing. Multiple dose clearance and half-life following q 12h dosing and q 24h dosing regimens were equivalent.

STUDY #7 An Ascending Single Dose Safety Study of Topiramate (RWJ-17021-000) in Healthy Men: Plasma Pharmacokinetics, Renal Excretion, Safety, and Tolerability (Protocol YA/CSS-82, Dec 1994).

OBJECTIVES: The objectives of this study were to assess the safety and acceptability of single oral doses of topiramate and to elucidate the topiramate pharmacokinetics including renal excretion. The study was conducted in 28 healthy male volunteers.

FORMULATION: 100 mg Tablet Batch No. R4198, Formula No. 1, manufactured by McNeil Pharmaceuticals at Spring House, PA.
Doses: Multiple units of 100 mg tablets.

STUDY DESIGN AND SAMPLING:

The study was a double-blind, placebo-controlled study. Subjects were divided into three groups of 12 each and were randomly assigned to receive topiramate or placebo. Within each group six subjects were assigned to receive topiramate and six placebo. Subjects who qualified for enrollment were assigned to one of three treatment groups. Group 1 received either 100 or 200 mg topiramate or placebo; Group 2 received either 400 or 800 mg topiramate or placebo; and Group 3 received 1200 mg of topiramate (n=4) or placebo (n=3). A washout period of 1 week separated the dose level treatments. Each group completed the study before the next group started. All treatment doses were given in

RESULTS:

Plasma: The study was terminated prematurely because of an adverse event and occurred in a subject receiving 1200 mg topiramate. As a result only four subjects received 1200 mg dose and none received 1600 mg dose. C_{max} and AUC data indicated a deviation from linearity at higher doses. As the dose was increased from 100 mg to 1200 mg, C_{max} and AUC were almost 40% and 56% higher at 1200 mg dose compared to 100 mg dose than it should be, had there been a linear relationship between the doses.

Urine: Approximately 23 and 34% of the administered dose was recovered in the urine at 16 and 32 h, respectively, after dosing. A linear and proportional relationship between the dose and the cumulative amount excreted at 16 and 32 h was observed in this

study over the dose range of 200-1200 mg. A slight deviation from proportionality occured between the 100 and 200 mg dose levels.

Plasma pharmacokinetics of Topiramate

Parameter	100 mg	2 x 100 mg	4 x 100 mg	8 x 100 mg	12 x 100 mg
C_{max} (µg/mL)	1.73 ± 0.22	3.68 ± 0.40	7.70 ± 0.80	18.38 ± 2.71	28.73 ± 3.22
T_{max} (h)	1.75 ± 1.17	1.42 ± 0.80	3.50 ± 0.55	4.33 ± 2.42	3.75 ± 1.71
AUC (0-32 h) (µg*h/mL	31.7 ± 4.2	73.1 ± 7.8	163.9 ± 26.1	360.0 ± 27.2	594.3 ± 42.4
V/F (L)	58.0 ± 11.7	55.5 ± 7.7	50.8 ± 7.4	43.8 ± 5.6	38.5 ± 4.1
CL/F (mL/min)	36.1 ± 3.5	28.5 ± 4.6	25.8 ± 5.1	23.2 ± 1.9	22.5 ± 2.4
$t_{1/2}$ (h)	18.7 ± 3.9	23.0 ± 5.0	23.0 ± 1.7	22.0 ± 3.2	20.0 ± 3.0

Values are reported as Mean ±SD

Urine pharmacokinetics of Topiramate

Parameter	100 mg	2 x 100 mg	4 x 100 mg	8 x 100 mg	12 x 100 mg
Cum amount [0-16 h]	15.99 ± 1.99	43.77 ± 8.82	87.63±15 .57	183.28 ± 17.36	310.18 ± 25.53
Urinary Excretion (% Dose) [0-16 h]	15.99 ± 1.99	21.88 ± 4.41	21.91 ± 3.89	22.91 ± 2.17	25.85 ± 2.13
Cum amount [0-32 h]	24.48 ± 3.59	65.48 ± 14.0	140.49 ± 16.60	ND	458.10 ± 82.30
Urinary Excretion (% Dose) [0-32 h]	24.48 ± 3.59	32.74 ± 7.00	35.12 ± 4.15	ND	38.17 ± 6.86
CL_R (mL/min)	13.05 ± 2.34	14.60 ± 2.51	14.46 ± 1.90	14.04 ± 1.58	12.95 ± 2.32

ND = Not Determined

CONCLUSIONS:

Topiramate is rapidly absorbed. Plasma C_{max} and AUC are not linearly related to dose. Cumulative urinary excretion amount is linearly and proportionally related to dose at doses from 200-1200 mg; the 100 mg dose deviated from this proportionality. Renal excretion of unchanged topiramate is a major pathway of elimination.

Comments:

This study has a serious designing flaw. Plasma and urine samples were collected till 32 hrs, which is just slightly over one half-life of topiramate. As a consequence, AUC (0-inf) could not be determined accurately, since plasma concentrations at 400, 800 and 1200 mg dose are much higher than the detection limit. As a result, extrapolation of AUC and calculation of oral clearance based upon this AUC will not reflect the true values of these parameters. Therefore, any conclusion from this study will be qualitative.

STUDY # 8: Evaluation of the Absorption, Excretion, and Biotransformation of a 100 mg Solution Dose of Topiramate-^{14}C in Healthy Male Volunteers (MS-177, June 1993).

OBJECTIVES:

The objectives of this study were:

(1) To evaluate the absorption and excretion of topiramate following oral administration of a 100 mg aqueous solution dose of topiramate-^{14}C to healthy male volunteers.

(2) To obtain the pharmacokinetic parameters of total radioactivity and topiramate in plasma and blood, to evaluate the amounts of topiramate excreted in urine, and to compare these results to those obtained with unlabeled topiramate.

(3) To obtain biotransformation profiles of topiramate in plasma, blood, urine, and fecal extracts.

(4) To isolate, identify, and quantify any significant metabolites of topiramate, where possible.

(5) To propose metabolic pathways for topiramate in man; to compare and contrast the proposed pathways with those obtained in animal species.

FORMULATION:

100 mg Aqueous solution ^{14}C Lot No. 6473-18, manufactured at Spring House, PA. Specific Activity 0.97 µCi/mg Total Radioactivity.

STUDY DESIGN AND SAMPLING:

The study was an open, single-dose study in which six healthy male subjects received 100 mL of an aqueous solution containing 100 mg of topiramate-^{14}C. Blood, urine, and fecal samples were collected for 240 hours (10 days) following treatment. The samples for total radioactivity and for topiramate were analyzed by liquid scintillation spectrometry and capillary GC using flame ionization detection, respectively.

RESULTS:

Unchanged topiramate accounted for 40% of the dose in the 0-48 hour urine sample and more than 85% of the sample in the 0.5-24 hour in plasma and blood, indicating that topiramate was not extensively metabolized and the renal excretion (81% of the dose) was the major route of elimination of the drug. A total of 81.3 ± 4.3% of the administered dose was recovered in excreta in 10-day period. In urine 80.6 ± 4.3% dose was excreted, whereas only 0.72 ± 0.3% dose was excreted in feces. Unchanged

topiramate accounted for 73% of the radioactivity in all excreta samples. Unchanged topiramate plus six trace (<5% of the sample) metabolites were isolated, characterized and identified from the plasma, urine, and feces in humans. The proposed pathway of these metabolites are hydroxylation, hydrolysis and glucuronidation.

Plasma, Urine and Fecal Pharmacokinetic Parameters

Parameter	100 mg Solution Total Radioactivity	100 mg Solution Topiramate
C_{max} (μg/mL)	2.38 ± 0.42	2.25 ± 0.48
T_{max} (h)	1.10 ± 0.7	0.83 ± 0.61
AUC (0-240 h) (μg*h/mL)	76.68 ± 6.24	63.10 ± 9.77
t1/2 (h)	91.00 ± 21.70	22.46 ± 6.14
CL/F (mL/min)	21.87 ± 1.96	26.95 ± 4.14
Urinary Excretion (% Dose) [0-240 h]	80.6 ± 4.3	59.3 ± 4.7
Fecal Excretion (% Dose) [0-120 h]	0.72 ± 0.30	ND

Values are reported as Mean ±SD . ND Not Determined

CONCLUSIONS:

Topiramate is rapidly absorbed and is not extensively metabolized. Six trace (<5% of the sample) metabolites were isolated, characterized and identified from plasma, urine, and feces from hydroxylation, hydrolysis, and glucuronidation metabolic pathways. Renal excretion is the major route of elimination of topiramate.

STUDY# 9: The Pharmacokinetics and Renal Excretion of Topiramate in Male and Female Subjects with Mild to Severe Renal Impairment and in Age, Sex, and Weight Matched Subjects with Normal Renal Function (DM-92340, October 1993).

OBJECTIVES:

The objective of this study was to determine the pharmacokinetics and renal excretion of topiramate in renally-impaired subjects (CL_{CR} <30 ml/min/1.73m^2, N=7 and CL_{CR} 30-69 ml/min/1.73m^2, N=7) as compared to subjects with normal renal function (CL_{CR} ≥70 ml/min/1.73m^2, N=14) following oral administration of one 100 mg tablet of topiramate.

FORMULATION: 100 mg Tablet Batch No. R4504, Formula No. 1, manufactured at Spring House, PA.

STUDY DESIGN AND SAMPLING:

This study was a single dose design in male and female subjects with renal impairment compared to subjects with normal renal function who were matched to the impaired subjects by gender, age, and weight. There were 3 males and 4 females in the group with creatinine clearance <30 ml/min/1.73m^2 and matched subjects with creatinine clearance >70 ml/min/1.73m^2. In the group of creatinine clearance 30-69 ml/min/1.73m^2, there was only one female along with 6 males and matched subjects with creatinine clearance >70 ml/min/1.73m^2. Blood samples were collected for 336 hours following each treatment. Urine samples were collected for 96 hours. Concentrations of topiramate in plasma and urine were analyzed by gas chromatographic method with nitrogen phosphorous detection.

Human plasma: Linearity: 0.1-10 µg/mL, Sensitivity: 0.1 µg/mL
Human urine: Linearity: 1.0-100 µg/mL , Sensitivity: 1.0 µg/mL

RESULTS:

The absolute bioavailability of topiramate, estimated from oral and renal clearance data was between 81 and 95%. However, the estimated bioavailability of topiramate using renal vs oral data has not been examined thoroughly, therefore the reported bioavailability may not be accurate.

The results show that the pharmacokinetics of topiramate in plasma and urine were affected by renal impairment, since almost 70% drug is excreted unchanged in urine. Oral clearance decreased by 56% in the severe group and by 46% in the moderate group as

compared to normals. A four-fold decrease in the severe group and two-fold decrease in the moderate group was observed for renal clearance as compared to normals.

Furthermore, the group of subjects in 30-69 ml/min creatinine clearance was divided into two (i) subjects with creatinine clearance 30-50 ml/min/1.73m^2 (n = 4) (ii) subjects with creatinine clearance 51-69 ml/min/1.73m^2 (n = 3). There was no difference in pharmacokinetic parameters between groups of subjects whose creatinine clearance ranged either from 30-50 ml/min/1.73m^2 or 51-69 ml/min/1.73m^2.

Accumulation of topiramate would be expected to occur in epileptic patients with renal impairment if chronically dosed at the same rate as patients with normal renal function, as the elimination half-life has also increased.

The mean pharmacokinetic parameters are summarized in the tables overleaf.

Plasma and Urine Pharmacokinetic Parameters

(N=7 for each group)

Parameters	100 mg Tablet CLCR <30	100 mg Tablet CLCR ≥70	100 mg Tablet CLCR 30-69	100 mg Tablet CLCR ≥70
C_{max} (µg/mL)	2.13 ± 0.25	2.24 ± 0.48	1.89 ± 0.75	1.60 ± 0.40
T_{max} (h)	1.6 ± 0.5	3.0 ± 4.0	1.1 ± 0.4	1.4 ± 0.8
AUC (0-∞) (µg*h/mL)	190.8 ± 49.9	88.1 ± 24.2	136.8 ± 45.6	73.8 ± 12.1
AUC (0-*) (µg*h/mL)	173.5 ± 49.9	81.8 ± 24.9	123.4 ± 41.4	64.0 ± 14.4
$t_{1/2}$ (h)	58.8 ± 11.2	31.6 ± 4.8	54.6 ± 11.2	37.5 ± 8.2
CL/F (mL/min)	9.24 ± 2.25	20.25 ± 5.83	13.38 ± 4.33	23.13 ± 3.97
CL/F (mL/min/kg)	0.12 ± 0.04	0.27 ± 0.06	0.15 ± 0.05	0.28 ± 0.06
Ur. Excr (% Dose)[0-96 h]	17.65 ± 3.53	45.94 ± 6.18	30.02 ± 11.16	44.98 ± 7.86
CL_R (mL/min)	2.54 ± 0.42	10.82 ± 2.32	6.18 ± 2.83	13.13 ± 2.80

Values are reported as Mean ±SD. * Last measured concentration.

Creatinine clearance in ml/min/1.73m^2

CONCLUSIONS:

Dosing: It is recommended that in renal failure patients (creatinine clearance ≤69 ml/min/1.73m^2) topiramate dose should be initiated at doses of 100 mg q.d. (normal dose = 100 mg b.i.d.) The maintenance dose in normals is 200-800 mg b.i.d., therefore, the recommended maintenance dose of topiramate in renally-impaired subjects (creatinine clearance ≤69)(is) 200-800 mg per day.

STUDY # 10: The Pharmacokinetics of Topiramate in Subjects with End-Stage Renal Disease Undergoing Hemodialysis (DM-92352, MS-221, October 1993).

OBJECTIVES: The objective of this study was to determine the pharmacokinetics of topiramate following administration of a single 100 mg oral dose in subjects with end-stage renal disease undergoing hemodialysis.

FORMULATION: 100 mg Tablet Batch No. R4561, Formula No. 37, manufactured at Dorado, Puerto Rico.

STUDY DESIGN AND SAMPLING:

This study was a single dose study to determine the pharmacokinetics of topiramate following oral administration in eight subjects with end-stage renal disease. Two subjects had significant protocol violations and were not considered in the data analysis. The remaining six subjects were from 25 to 43 years of age and ranged in weight from 117 to 209 pounds. Venous blood samples were collected just prior to topiramate administration and at selected time points to 104 hours after dosing (1,, 2, 3, 6, 10, 16, 24, 36, 37, 38, 40, 48, 72, and 104 hours). Arterial blood samples were collected during the hemodialysis period at 32, 33, 34, and 35 hours after dosing. Dialysate fluid samples were collected prior to hemodialysis and for the intervals 32-33, 33-34, and 34-35 hours after dosing (total of 3 hours sampling). Whole blood, plasma and dialysate fluid samples were analyzed for topiramate by validated gas chromatographic methods with nitrogen phosphorous detection.
Human plasma: Linearity: 0.5-50 µg/mL ; Sensitivity: 0.5 µg/mL
Dialysate Fluid: Linearity: 0.5-50 µg/mL ; Sensitivity: 0.5 µg/mL

RESULTS:

Topiramate was effectively removed from the plasma by hemodialysis. Over 3 hr hemodialysis about 19 mg of topiramate was removed from the body. The mean hemodialysis clearance of topiramate from plasma was increased approximately 11 times over the mean clearance of topiramate from plasma of the same subjects when they were not on hemodialysis. The mean pharmacokinetic parameters (n = 6) are summarized in the table below.

Plasma Pharmacokinetic Parameters

Parameter	100 mg Tablet Plasma	100 mg Tablet CL_{cr} >70 (ml/min)
C_{max} (μg/mL)	1.92 ± 0.48	1.60 ± 0.40
T_{max} (h)	1.8 ± 1.0	1.4 ± 0.8
AUC (0-32 h) (μg*h/mL)	45.5 ± 8.1	-
AUC (0-∞) (μg*h/mL)	166.8 ± 49.8	73.8 ± 12.1
t1/2 (h)	78.4 ± 27.5	37.5 ± 8.2
Dialysis Recovery[a] mg [32-35 h]	18.67 ± 1.83	ND
CL/F(mL/min)	10.8 ± 3.4	23.13 ± 3.97
CL_D[b] (mL/min) [32-35 h]	123.5 ± 15.7	-

Values are reported as Mean ±SD ND Not Determined

[a] Amount of topiramate removed from the body by dialysis. [b] Hemodialysis plasma clearance.

CONCLUSIONS:

Topiramate is removed by hemodialysis, resulting in a 50% decrease in plasma concentrations. Titration of topiramate doses is recommended at the time of hemodialysis.

STUDY # 11: Evaluation of the Pharmacokinetics of Topamax™ (Topiramate) in Male and Female Subjects with Moderate to Severe Hepatic Impairment and in Healthy Subjects Matched by Age, Sex, and Weight (MS-209, October, 1993).

OBJECTIVES:

The objective of this study was to determine the effect of impaired hepatic function on the pharmacokinetics of a single 100 mg oral dose of topiramate administered in the fasted state to subjects with moderate to severe hepatic impairment and in healthy control subjects matched by age, weight, and sex.

FORMULATION: 100 mg Tablet Batch No. R4539, Formula No. 37, manufactured at Dorado, Puerto Rico.

STUDY DESIGN AND SAMPLING:

The study was a single dose study in two male and three female subjects with hepatic impairment (Child-Pugh Index 5-9) and in six healthy controls matched to the hepatically-impaired subjects by age, gender, and weight. The subjects ranged in age from 37 to 48 years and weighed from 141.5 to 226.6 pounds. Blood and urine samples were collected for 168 and 96 hours, respectively following administration of topiramate. Plasma and urine samples were analyzed for topiramate by validated gas chromatographic methods with nitrogen phosphorous detection.

Human plasma: Linearity: 0.5-50 µg/mL , Sensitivity: 0.5 µg/mL
Urine: Linearity: 1.0-100.0 µg/mL ; Sensitivity: 1.0 µg/mL

RESULTS:

The results of the study indicate that in hepatically impaired subjects C_{max} and AUC of topiramate increased by 29%, whereas there was a 29% decrease in oral clearance (0.27 vs 0.38 ml/min/kg). The renal clearance was measured only in three subjects. There was no difference in non-renal clearance between the two groups, but renal clearance in hepatically impaired subjects decreased by 50%. Since initiation of all antiepileptic drugs in epileptic patients begins with a fixed dose and then is titrated to tolerable effective doses, the topiramate dose is recommended to be titrated in this fashion. The moderate increase in C_{max} and AUC in hepatically impaired subjects may not be of any clinical significance and there might not be any need to adjust topiramate dose in epileptic patients with liver impairment.

The mean pharmacokinetic parameters are summarized in the table below.

Plasma Pharmacokinetic Parameters

Parameter	100 mg Tablet Hepatically- Impaired	100 mg Tablet Healthy Matches
C_{max} (µg/mL)	2.23 ± 1.17	1.73 ± 0.21
T_{max} (h)	1.95 ± 2.35	1.83 ± 1.43
AUC (0-*) (µg*h/mL)	43.9 ± 11.9	34.8 ± 12.1
AUC (0-∞) (µg*h/mL)	72.2 ± 10.3	55.9 ± 15.5
t1/2 (h)	33.61 ± 10.7	24.65 ± 4.99
Ur. Excr [0-96 h]	39.64 ± 4.75	44.01 ± 0.45
CL/F (mL/min)	23.45 ± 3.27	31.78 ± 8.93
CL/F (mL/min/kg)	0.27 ± 0.05	0.38 ± 0.08
CL_R (mL/min)	13.49 ± 3.44	26.44 ± 6.03
CL_{NR} (mL/min)	7.85 ± 1.51	8.09 ± 5.30

Values reported as Mean ±SD * Last measured concentration.

CONCLUSIONS:

Hepatically-impaired subjects had a 29% increase in C_{max} and $AUC_{(0-\infty)}$ of topiramate. The decreased oral clearance of topiramate (29%) was primarily due to decreased renal clearance (49%). Nonrenal clearance was unchanged.

Dosing: A 29% decrease in oral clearance of topiramate in the hepatically impaired group does not warrant dosage adjustment.

STUDY #12 : A Comparative Study of the Steady-State Pharmacokinetics of Phenytoin (Dilantin® Kapseals® Brand) and of Topamax™ (Topiramate) in Male and Female Epileptic Patients on Monotherapy and During Combination Therapy (Study # MS 215, 26 October, 1993).

OBJECTIVES:

The objectives of this study were to investigate:

(1) the steady-state pharmacokinetics of phenytoin during phenytoin monotherapy,

(2) the steady-state pharmacokinetics of phenytoin at each of three escalating concomitant topiramate doses,

(3) the steady-state pharmacokinetics of topiramate during topiramate monotherapy, and

(4) the steady-state pharmacokinetics of topiramate at each of three escalating topiramate doses during concomitant fixed dose phenytoin therapy.

FORMULATIONS:

Topiramate:

100 mg Tablet Batch No. R4561, Formula No. 37,
200 mg Tablet Batch No. R4562, Formula No. 47, and
400 mg Tablet Batch No. R4563, Formula No. 36;
all manufactured at Dorado, Puerto Rico.

Phenytoin:

DILANTIN^R KAPSEALS^R brand of sodium phenytoin in 30 mg and 100 mg capsules.

STUDY DESIGN AND SAMPLING:

The study was an open, escalating dose study conducted in 12 epileptic patients (7 men, 5 women). The patients were stabilized on phenytoin monotherapy (130-300 mg q12h or 360-480 mg q24h; n = 6 in each group). The 30 and 100 mg capsule strengths of DILANTIN^R brand of phenytoin was used. The topiramate dose escalation began with concomitant topiramate 100 mg qPM for 3 days, followed by 100 mg q12h for at least 11 days. Dose escalation continued by administration of topiramate 100 mg qAM and 200 mg qPM for 3 days followed by 200 mg q12h for at least 11 days. Dose escalation was completed by administration of topiramate 200 mg qAM and 400 mg qPM for 3 days followed by 400 mg q12h for at least 11 days. After two weeks of stabilization on the maximium tolerated concomitant topiramate dose, phenytoin doses were reduced by 25% at intervals of 1 week over the next 4 weeks. This was continued until patients were on topiramate monotherapy or on the lowest achievable phenytoin dose. After at least 2 weeks

on the final dosage regimen, patients were allowed to enter a long term extension protocol; otherwise, topiramate doses were to be decreased in decrements of no more than 200 mg/day at intervals of at least 1 week.

Serial blood and urine samples were collected during the baseline phenytoin monotherapy period; during the concomitant topiramate dose escalation period; after stabilization at the maximum concomitant topiramate regimen; and after achieving topiramate monotherapy or the lowest possible concomitant dose of phenytoin. For patients on the q12 h phenytoin dosing schedule, 10 ml blood samples were collected following the administration of phenytoin and/or topiramate at time 0, 1, 2, 3, 4, 6, 9, and 12 hrs, whereas urine samples were collected for the intervals from 0-6 and 6-12 hours postdosing. For patients on the q24 h phenytoin, blood samples were collected at time 0, 1, 2, 3, 4, 6, 9, 12, 16 and 24 hrs, whereas urine samples were collected for the intervals from 0-6, 6-12 and 12-24 hours postdosing. Plasma and urine samples for topiramate, and total and unbound plasma concentrations of phenytoin were analyzed by validated analytical methods.

RESULTS:

(i) Influence of Topamax on phenytoin:

The effect of concomitant topiramate therapy on the steady state pharmacokinetics of total and unbound phenytoin was as follows:

Unbound phenytoin: Nine of the 12 patients had mean AUC_{SS} ratios (combination therapy/ monotherapy) for unbound phenytoin of 1.19 (range 1.04-1.45), suggesting that there was a decrease in phenytoin clearance in this group of patients. The remaining three patients had a mean AUC_{SS} ratio of 0.93 (range 0.87-0.97).

Total phenytoin: Almost similar pattern was observed with total phenytoin AUC_{SS} ratios as seen for unbound phenytoin.

(ii) Influence of phenytoin on Topamax:

Over the dose range of 100-400 mg q12h, topiramate exhibited linear kinetics. Topiramate oral clearance was increased by 2.5 fold during combined therapy with phenytoin as compared to topiramate resulting in decreased steady-state plasma topiramate concentrations. This decrease might be due to the induction of topiramate metabolism by phenytoin.

Topiramate Plasma Pharmacokinetic Parameters (q 12hrs) during concomitant Phenytoin therapy

Parameters	100 mg Steady State	200 mg Steady-State	400 mg Steady-State	400 mg Top Mono
C_{max} (µg/mL)	4.12 ± 0.96	7.58 ± 1.85	12.6 ± 2.42	25.8 ± 4.34
T_{max} (h)	1.33 ± 0.49	1.40 ± 0.70	1.43 ± 0.53	2.25 ± 0.96
AUC_{ss} (0-12 h) (µg*h/mL)	31.81 ± 7.45	60.85 ± 16.38	104.95 ± 20.1	253.53 ± 31.56
CL/F (mL/min)	55.0 ± 12.33	58.40 ± 14.70	65.14 ± 9.95	26.64 ± 3.70
$C_{av(ss)}$ (µg/mL)	2.65 ± 0.62	5.07 ± 1.37	8.75 ± 1.67	21.13 ± 2.63

Mean ±SD.

CONCLUSION:

The results of this study indicate that topiramate may decrease phenytoin clearance by 20% in patients resulting in higher phenytoin plasma concentrations. However, due to the small sample size it is difficult to make a definite conclusion. Therefore, it is recommended that patients be regularly monitored for their clinical progress when combination therapy with topiramate is initiated.

Topiramate clearance increased by 2.5 fold during combination therapy with phenytoin, resulting in lower plasma topiramate concentrations as compared to topiramate

Therefore, topiramate dosing regimen may require adjustment when administered with phenytoin.

STUDY #13: A Comparative Study of the Steady-State Pharmacokinetics of Carbamazepine (Tegretol®) and Topamax™ (Topiramate) in Male and Female Epileptic Patients on Monotherapy, and During Combination Therapy (Study # MS 216, October, 1993).

OBJECTIVES:

The objectives of this study were to determine within patients with partial epilepsy: (1) the steady-state pharmacokinetics of carbamazepine during carbamazepine

(2) the steady-state pharmacokinetics of carbamazepine during concomitant therapy with three escalating topiramate doses,
(3) the steady-state pharmacokinetics of topiramate at each of three escalating topiramate doses while receiving a fixed dose of carbamazepine, and
(4) the steady-state pharmacokinetics of topiramate while on fixed doses of topiramate

FORMULATIONS:

Topiramate:

100 mg Tablet Batch No. R4561, Formula No. 37,
200 mg Tablet Batch No. R4562, Formula No. 47, and
400 mg Tablet Batch No. R4563, Formula No. 36;
all manufactured at Dorado, Puerto Rico.

Carbamezapine:

TEGRETOL^{R} brand of carbamazepine provided by the investigator.

STUDY DESIGN AND SAMPLING:

The study was an open titration study in 12 patients (study schedule attached). The study began with a 3-week baseline period (carbamazepine). Patients remained on established CBZ therapy as the topiramate dose escalation began with concomitant topiramate 100 mg qPM for 3 days, followed by 100 mg q12h for 11 days. Dose escalation continued by administration of topiramate 100 mg qAM and 200 mg qPM for 3 days followed by 200 mg q12h for 11 days. Dose escalation was completed by administration of topiramate 200 mg qAM and 400 mg qPM for 3 days followed by 400 mg q12h for 11 days. After two weeks of stabilization on the maximium tolerated concomitant topiramate dose, carbamazepine doses were reduced by 25% at intervals of 1 week over the next 4 weeks. This was continued until patients were on topiramate

or on the lowest achievable carbamazepine dose along with topiramate. After additional 2 weeks on the final dosage regimen, patients were allowed to enter a long term extension protocol; otherwise, topiramate doses were to be decreased in decrement of 200 mg b.i.d. at intervals of at least 1 week.

Serial blood samples (10 ml) were collected for 8 hours during the baseline carbamazepine monotherapy over 3-week period at time 0, 1, 2, 3, 4, 6, and 8 hrs. Blood samples were obtained in the topiramate dose escalation period (end of weeks 2, 4, 6) and at the end of carbamazepine dose reduction period (end of week 11) at time 0, 1, 2, 3, 4, 6, 8, and 12 hrs. During the three-week baseline carbamezapine period, urine samples were collected for the 0-4 and 4-8 hour time intervals after the morning carbamazepine dose. Urine samples were also collected at the 0-4, 4-8, 8-12 hour time intervals after the morning topiramate dose at the end of weeks 2, 4, 6, and 11. Plasma and urine samples for topiramate, and total and unbound plasma concentrations of carbamazepine and its epoxide metabolite were analyzed by validated analytical methods.

RESULTS:

Carbamazepine pharmacokinetics:

The results of the study indicate that total carbamazepine pharmacokinetics remains unchanged during concomitant administration of topiramate doses of 100-400 mg b. i. d. Similar results were obtained for unbound carbamazepine and for total and unbound carbamazepine epoxide. The pharmacokinetic parameters of carbamazepine have been summarized in the tables.

Topiramate pharmacokinetics:

Topiramate exhibited linear kinetics over 100-400 mg b.i.d. dose when administered concomitantly with carbamazepine doses of 300 to 800 mg q8h. Since only three patients achieved monotherapy on topiramate, statistical comparison between monotherapy of topiramate and co-administration with carbamazepine was not appropriate. However, the overall result was a 40% decrease in topiramate $AUC_{(0-12)}$, C_{max}, C_{avg} and $Cmin_{(0)}$ during concomitant carbamazepine therapy than during topiramate monotherapy. Topiramate total clearance was almost two fold higher during concomitant carbamazepine therapy as compared to monotharapy. Though there was no change in renal clearance of topiramate between mono and concomitant therapy, there was almost 40% decrease in unchanged topiramate excretion in urine following concomitant administration with carbamazepine. A 3-fold increase in nonrenal clearance indicates that

the metabolic clearance of topiramate increases with concomitant administration of carbamazepine.

The mean pharmacokinetic parameters of topiramate are summarized in the table below.

Topiramate Plasma and Urine Pharmacokinetic Parameters

Parameters	100 mg b.i.d Top + CBZ	200 mg b.i.d Top + CBZ	400 mg b. i.d. Top + CBZ	Week 6 400 mg Top + CBZ	Topiramate Mono 400 mg
C_{max} (µg/mL)	4.6 ± 0.6	8.2 ± 1.2	15.5 ± 3.3	3.4 ± 1.4 [a]	5.5 ± 0.6 [a]
T_{max} (h)	1.1 ± 0.3	1.6 ± 1.1	1.2 ± 0.6	1.0 ± 1.0	1.7 ± 0.6
AUC(0-12 h) (µg*h/mL)	37.8 ± 6.9	70.3 ± 11.6	132.9 ±28.3	30.5 ± 12.3 [a]	51.1 ±8.0 [a]
C_{min} (0) (µg/mL)	2.3 ± 0.7	4.4 ± 1.0	8.7 ± 1.6	2.2 ± 0.4 [a]	3.7 ± 0.9 [a]
C_{avg} (µg/mL)	3.1 ± 0.6	5.9 ± 1.0	11.1 ± 2.4	2.5 ± 1.0 [a]	4.3 ± 0.7 [a]
Ur.Excretion (% Dose) [0-12h]	33.9±9.6	36.7±11.9	33.1±10.1	32.3±15.4	55.7±16.4
CL/F (mL/min)	45.6 ± 8.8	48.5 ± 7.5	53.5 ± 18.0	63.7 ± 33.5	33.2 ± 4.8
CL_R (mL/min)	15.5±6.1	17.4±5.4	17.4±5.7	19.3±9.0	18.0±3.0

Mean ±SD. [a] Normalized to a 100 mg b.i.d. topiramate dose.

CONCLUSIONS:

The study indicates that concomitant administration of topiramate with carbamazepine does not alter the pharmacokinetics of carbamazepine and its epoxide. Therefore, carbamazepine dosage adjustment may not be necessary when given with topiramate (topiramate dose = 100-400 mg b. i. d.).

The steady-state topiramate plasma pharmacokinetics are linear and dose proportional over the 100-400 mg b.i.d. dose range when given as adjunctive therapy to carbamazepine. Topiramate clearance with CBZ was increased by 2-fold compared to its clearance in monotherapy. Therefore, to maintain equivalent topiramate concentrations during concomitant therapy with carbamazepine, the topiramate dose may need to be doubled. However, the clinical condition of the patients should also be monitored to optimize topiramate dose.

STUDY #14: A Comparative Study of the Steady-State Pharmacokinetics of Valproic Acid (Depakote® Brand) and of Topamax™ (Topiramate) in Male and Female Epileptic Patients on and During Combination Therapy (Study # MS 218, October, 1993).

OBJECTIVES: The objectives of this study were to determine:

(1) the steady-state pharmacokinetics of valproic acid during valproic acid monotherapy,

(2) the steady-state pharmacokinetics of valproic acid during concomitant therapy with three escalating topiramate doses,

(3) the steady-state pharmacokinetics of topiramate at each of three escalating topiramate doses while on a fixed dose valproic acid therapy, and

4) the steady-state pharmacokinetics of topiramate while on fixed doses of topiramate monotherapy.

FORMULATION:

Topiramate:

100 mg Tablet Batch No. R4561, Formula No. 37,

200 mg Tablet Batch No. R4562, Formula No. 47, and

400 mg Tablet Batch No. R4563, Formula No. 36;

all manufactured at Dorado, Puerto Rico.

Valproic acid:

Depakote^{R} brand of valproic acid, from a single lot of commercially available product, supplied by the investigators.

STUDY DESIGN AND SAMPLING:

The study was an open, escalating dose study conducted in 12 epileptic patients (6 men, 6 women). Topiramate and/or valproic acid were administered 1 hour before or two hours after meals (dosing scheme attached). The study began with a three-week baseline period in patients with partial epilepsy who were stabilized on valproic acid (500 to 2250 mg b. i. d.). Patients continued on their established valproic acid dosing regimen during topiramate dose escalation. The topiramate dose escalation began with concomitant topiramate 100 mg qPM for 3 days, followed by 100 mg q12h for 11 days. Dose escalation continued by administration of topiramate 100 mg qAM and 200 mg qPM for 3 days followed by 200 mg q12h for 11 days. Dose escalation was completed by administration of topiramate 200 mg qAM and 400 mg qPM for 3 days followed by 400 mg q12h for at least 11 days. After two weeks of stabilization on the maximum tolerated concomitant topiramate dose, valproic acid doses were reduced by 25% at intervals of 1

week over the next 4 weeks. This was continued until patients were on topiramate or on the lowest achievable valproic acid dose. After an additional 2 weeks on the final dosage regimen, patients were allowed to enter a long term extension protocol; otherwise, topiramate doses were to be decreased in decrements of no more than 200 mg/day at intervals of at least 1 week.

Ten ml venous blood samples were collected after the morning valproic acid dose during the 3-week baseline valproic acid monotherapy period at time 0, 1, 2, 3, 4, 6, 9, and 12 hrs. Same sampling scheme was maintained during the concomitant topiramate dose escalation period and at the end of the valproic acid dose reduction period. In addition, a morning predose blood sample for trough topiramate concentrations was obtained weekly during the valproic acid dose reduction period, just prior to the next valproic acid dose reduction (i.e. at the start of weeks 8, 9, and 10).

RESULTS:

Topiramate pharmacokinetics:

Between 100 to 400 mg b.i.d. dosing, both C_{max} and $AUC_{(0-12)}$ were 25% less than expected (slightly non-linear) at the 400 mg b.i.d. dose. Topiramate plasma C_{max} and $AUC_{(0-12)}$ were reduced by 15% during concomitant steady-state valproic acid therapy. Topiramate oral clearance was increased in the presence of valproic acid by 15%, whereas its renal clearance and urinary recovery remained unaffected in the presence or absence of valproic acid. However, these small differences in topiramate pharmacokinetics may not be of any clinical significance.

Valproic acid pharmacokinetics:

There was approximately 13% increase in valproic acid oral clearance when given with 400 mg b. i. d. dose of topiramate as compared This was the maximum change in oral clearance for valproic acid and was seen with the highest dose of topiramate. No difference was noted for C_{max}, C_{min} and percent of dose excreted in urine of valproic acid given alone or with topiramate.

The mean pharmacokinetic parameters are summarized in the table below.

Steady-State Plasma and Urine Topiramate Pharmacokinetic Parameters

Parameters	100 mg b.i.d. + VA	200 mg b.i.d + VA	400 mg b.i.d. + VA	400 mg b.i.d. + VA (week 6)	400 mg Topiramate Monotherapy
C_{max} (µg/mL)	7.8 ± 1.4	14.1 ± 1.9	23.9 ± 2.9	5.8 ± 0.8[a]	6.8 ± 1.1[a]
T_{max} (h)	1.2 ± 0.4	1.8 ± 1.0	1.6 ± 1.0	1.9 ± 1.1	1.6 ± 1.3
AUC (0-12) (µg*h/mL)	76.8 ± 13.3	141.9 ±23.2	237.4 ±29.1	55.8 ± 8.0[a]	66.2 ± 11.8[a]
Ur.Excr. (% Dose) [0-12 h]	60.8 ± 15.9	55.0 ± 22.3	37.9 ± 10.9	41.4 ± 6.0	44.4 ± 7.1
CL/F (mL/min)	22.3 ± 4.2	24.1 ± 4.3	28.5 ± 3.7	29.8 ± 4.2	25.9 ± 4.6
CL_R (mL/min)	13.7 ± 5.0	12.9 ± 4.3	11.0 ± 4.1	12.4 ± 2.7	11.6 ± 3.2
C_{min} (ss) (µg/mL)	5.5 ± 1.1	10.0 ± 1.8	16.5 ± 2.3	3.9 ± 0.6[a]	4.6 ± 0.9[a]

Values are reported as Mean ±SD. [a] Normalized to a 100 mg b.i.d. topiramate dose.

Conclusion:

This study indicates that VPA increases the clearance of topiramate by 15% when the highest dose of topiramate was administered (400 mg b.i.d.). In turn, 400 mg b.i.d. dose of topiramate showed a 13% increase in the clearance of VPA.

STUDY #15: Steady-State Topiramate Pharmacokinetics in Patients with Partial Epilepsy Following Twice Daily Oral Dosing of Topiramate as Adjunctive Therapy to Phenytoin or Valproic Acid (Protocol YZL/CSS-102, October, 1993).

OBJECTIVES:

The objective of this study was to evaluate the safety, possible anticonvulsant drug interactions, and pharmacokinetics of oral topiramate given in two equally divided daily doses, as adjunctive therapy in patients with partial epilepsy who were stabilized on an optimum dose of either phenytoin (200-730 mg/day) or valproic acid (1000-3500 mg/day).

FORMULATION:

50 mg Tablet Batch No. R4325, Formula No.2 and
100 mg Tablet Batch No. R4324, Formula No.1, both manufactured at McNeil Pharmaceuticals, Spring House, PA.
Phenytoin and valproic acid were supplied by the investigator.

STUDY DESIGN AND SAMPLING:

This was an open titration study in which 13 patients took part. Ten patients (5 males, 5 females) had evaluable pharmacokinetic data and are considered in the data analysis. Following a 2-week baseline period of either phenytoin 200-730 mg/day or valproic acid 1000-3500 mg/day and while continuing on their established concomitant anticonvulsant dosing regimen, patients were started on topiramate 100 mg b. i. d. for 2 weeks. The topiramate dose was titrated up to their maximum tolerated dose, not to exceed 600 mg b.i.d. Doses were titrated in increments of 100 mg over an 8-week period (topiramate titration schedule attached). Patients were then maintained at the maximum tolerated topiramate dose for an additional 8 weeks (stabilization period). Pharmacokinetics were evaluated while at steady-state on 100 and 300 mg b.i.d. dose and at the end of the stabilization period (days 21, 42, 70, and 126). Topiramate pharmacokinetic parameters were assessed using data obtained at the 100 and 300 mg b.i.d. doses only, since the number of patients with data at other topiramate doses was limited to one patient on each

RESULTS:

Topiramate exhibited dose proportional pharmacokinetics when given along with phenytoin or valproic acid. The AUC(0-12), C_{max}, $C_{min}(0)$, and $C_{min}(12)$ were lower by approximately 2.5, 2, 3, 3 folds in group of patients who received concomitant phenytoin than in patients receiving valproic acid. Oral clearance was about 2.4 fold higher in patients receiving phenytoin than valproic acid, though renal clearance was unchanged in both the groups. The percent of topiramate dose excreted in urine was almost two fold higher in the group of patients who received concomitant valproic acid than the group receiving phenytoin. The result suggests that there is an increase in the metabolic clearance of topiramate in the presence of phenytoin.

Conclusion:

A 2 fold decrease in C_{max} and 2.5 fold decrease in AUC (0-12) was observed when topiramate was administered concomitantly with phenytoin as compared to concomitant administration with valproic acid. Furthermore, oral plasma clearance of topiramate increased by 2.4 fold with concomitant phenytoin. Based upon these results, there will be a need for topiramate dose adjustment when given with phenytoin, i. e. a higher dose of topiramate will be required.

Comments:

This study does not provide information on the effect of topiramate on phenytoin or valproic acid.

STUDY #16: Topiramate Pharmacokinetics in Patients with Partial Epilepsy Receiving Topiramate As Adjunctive Therapy to Carbamazepine Therapy. (Protocol YZT (CSS-103), Nov, 1993).

OBJECTIVES: The objective of this study was to evaluate the pharmacokinetics of topiramate in patients with partial epilepsy receiving topiramate as an adjunct therapy to carbamazepine therapy.

FORMULATION:

50 mg Tablet Batch No. R4325, Formula No. 2 and
100 mg Tablet Batch No. R4324, Formula No. 1, both manufactured at Spring House, PA. Carbamazepine was supplied by the investigator.

STUDY DESIGN AND SAMPLING:

Six males and two females took part in this study. The patients were on a 2-week baseline monotherapy of carbamazepine. Topiramate dosing was initiated at 100 mg single dose followed by 100 mg b .i. d (see attached scheme). The scheduled titration of topiramate dosage was increased at 1 or 2 week intervals in increment of 100 mg (every 12 hour dosing) upto tolerated dose not to exceed 600 mg b.i.d. The final pharmacokinetic profile was obtained at the end of the 8-week stabilization period at the highest tolerated dose of topiramate (CBZ dosing continued alongside). Pharmacokinetic parameters were evaluated following the first 100 mg single dose and at steady state on 100, 300, and 600 mg b.i.d. topiramate dosing. Blood and urine samples were collected for 72 hours following the first dose of topiramate and for 12 hours following all other doses. Blood, plasma and urine concentrations of topiramate were analyzed by a validated capillary gas chromatographic method. Carbamazepine plasma trough levels were collected at the time of the admission screen, during the baseline period, during the stabilization period and at study termination.

RESULTS:

At steady state topiramate doses over 100 to 600 mg b. i. d. range were linear in the presence of CBZ, and no statistical differences were found in pharmacokinetic parameters across the normalized doses.

The mean pharmacokinetic parameters are summarized in the table below.

Plasma and Urine Topiramate Pharmacokinetic Parameters

Parameters	100 mg Single Dose + CBZ	100 mg b.i.d. Steady-State + CBZ	300 mg b.i.d. Steady-State + CBZ	600 mg b.i.d.[a] Steady-State + CBZ
N	8	8	6	4
C_{max} (µg/mL)	1.87 ± 0. 62	4.66 ± 0.421	13.4 ± 2.76	26.2 ± 3.96
T_{max} (h)	1.17 ± 1.05	1.38 ± 0.52	1.25 ± 0.42	1.13 ± 0.63
AUC (0-∞) (µg*h/mL)	31.4 ± 10.7	ND	ND	ND
AUC (0-12 h) (µg*h/mL)	ND	39.5 ± 3.32	114.2 ± 16.2	225.2 ± 29.3
CL/F (mL/min)	59.2 ± 21.3	42.5 ± 3.53	44.4 ± 5.60	45.0 ± 6.10
Ur.Excr (% Dose) [0-12 h]	26.6[b] ± 12.6	37.2[b] ± 8.41	32.6 ± 14.7	39.45 ± 15.64
CL_R (mL/min)	19.2[b] ± 10.7	15.7[b] ± 3.13	14.4 ± 6.56	17.1 ± 4.70

Values are reported as Mean ±SD. ND = Not Determined

[a]At the end of the stabilization period

[b]The data from Subject 8 was excluded because of missing urinary excretion data.

Comments:

The steady-state topiramate plasma pharmacokinetics are linear and dose proportional over the 100-600 mg b.i.d. dose range when given as adjunctive therapy to carbamazepine. The effect of topiramate on CBZ and its metabolite (CBZ-epoxide) was not studied.

STUDY #17: Topiramate Pharmacokinetics in Patients with Partial Epilepsy Receiving Topiramate as Adjunctive Therapy to Primidone or Phenobarbital Therapy. (Protocol YZW (CSS-104), Oct 1993).

OBJECTIVES: The objective of this study was to evaluate the pharmacokinetics of topiramate in patients with partial epilepsy receiving topiramate as adjunctive therapy to primidone or phenobarbital therapy.

FORMULATION:

50 mg Tablet Batch No. R4325, Formula No. 2 and
100 mg Tablet Batch No. R4328, Formula No. 1; both manufactured at Spring House, PA. The investigators supplied primidone and phenobarbital (no mention of batch No).

STUDY DESIGN AND SAMPLING:

This was an open, ascending dose study in six patients. The patients were on a 2-week baseline monotherapy of primidone or phenobarbital, and topiramate dosing was initiated at 100 mg q a.m. for 1 week followed by 100 mg b .i. d. for two weeks. The scheduled titration of topiramate dosage was increased at 2 week intervals in increments of 100 mg every 12 hrs upto maximum tolerated dose not to exceed 600 mg b.i.d. The final pharmacokinetic profile was obtained at the end of the 8-week stabilization period at the highest tolerated dose of topiramate (please see attached dosing scheme). Pharmacokinetics were evaluated following topiramate administration of 100, 300, and 600 mg b.i.d. Blood and urine samples were collected for 72 hours following all three doses. Topiramate plasma trough levels were obtained on study days 0-7 and at each titration phase visit. Blood, plasma and urine concentrations of topiramate were analyzed by a validated capillary gas chromatographic method.

RESULTS:

The two patients who were supposed to receive phenobarbital dropped out of the study. Therefore, the results discussed below are for patients on primidone. The results of this study indicate a rapid absorption of topiramate in the presence of primidone, with peak concentrations reaching between 1-2 hours. AUC (0-12 h) appears to be proportional between 100 to 600 mg topiramate dose. The oral clearance does not change significantly across doses.

The mean pharmacokinetic parameters are summarized in the tables below.

Plasma and Urine Topiramate Pharmacokinetic Parameters

Parameters	100 mg b.i.d.	300 mg b.i.d.	600 mg[a] b.i.d.
N	2	3	2
C_{max} (µg/mL)	4.01 ± 0.714	10.5 ± 2.61	21.5 ± 1.00
T_{max} (h)	1.21 ± 1.12	1.83 ± 1.89	1.25 ± 0.354
AUC (0-12 h) (µg*h/mL)	30.8 ± 4.24	91.2 ± 9.86	166 ± 15.1
Ur.Excr (% Dose) [0-12 h]	24.2 ± 10.8	19.0 ± 13.6	28.6 ± 5.44
CL/F (mL/min)	54.7 ± 7.54	55.3 ± 5.99	60.6 ± 5.49
CL_R (mL/min)	12.8 ± 4.09	10.0 ± 6.34	17.5 ± 4.88

Values are reported as Mean ±SD. [a] At the end of the stabilization period.

This study does not mention the effect of topiramate on the pharmacokinetics of primidone or phenobarbital due to inconsistent trough levels of primidone and its active metabolite phenobarbital (please see attached figures).

Comments:

Topiramate exhibited linear kinetics from 100 to 600 mg b.i.d. However, the number of patients studied was small to evaluate pharmacokinetics of topiramate given as an adjunct to primidone. Due to the inconsistent trough levels of primidone and its active metabolite (phenobarbital), it was not possible to assess the effect of topiramate on the pharmacokinetics of primidone.

STUDY #18: A Pharmacokinetic Study to Evaluate Coadministration of Digoxin and Topiramate in Healthy Male Volunteers (MS-219, Oct, 1993).

OBJECTIVES: The objective of this study was to evaluate the potential for a pharmacokinetic interaction between topiramate and digoxin.

FORMULATION:

100 mg Topiramate Tablet Batch No. R4561, Formula No. 37, manufactured at Dorado, Puerto Rico. Digoxin Capsules (0.2 mg (highest strength), Lanoxicaps^{R} (soft gel capsule), Lot No: 1W5007, Burroughs Wellcome Co.)

STUDY DESIGN AND SAMPLING:

This was an open, sequential, two-period, two-treatment study in which the effect of pretreatment with a 100 mg b.i.d. oral regimen of topiramate for 6 days on the pharmacokinetics of a 0.6 mg single oral dose of digoxin was studied in 12 healthy male subjects.

Treatment A: Subjects received a single, oral 0.6 mg dose of digoxin as three 0.2 mg digoxin capsules on day 1. The subjects were fasted overnight for 12 hours.

Treatment B: On the morning of the eighth day after receiving treatment A, subjects received a single 100 mg oral dose of topiramate followed the next morning by a 100 mg b. i. d. regimen of topiramate for 9 days. After a 12-hr overnight fast following the 13th dose of the topiramate multiple dose regimen, subjects received a second single oral, 0.6 mg dose of digoxin as three 0.2 mg digoxin capsules. The duration of the study was 19 days for each subject. Blood and urine samples were collected for 72 hours after each digoxin dose for measurement of plasma topiramate concentrations and/or for

RESULTS:

Digoxin: The results of this study indicate that both C_{max} and AUC $_{(0\text{-inf})}$ of digoxin decreased by 16% and 12%, respectively in the presence of topiramate. Pretreatment of digoxin with topiramate did not affect t_{max} or $t_{1/2}$ of digoxin. Oral clearance of digoxin increased by 13% in the presence of topiramate. It should be noted

that digoxin was given to healthy volunteers as a single oral dose and the study does not provide information on the effect of digoxin on the pharmacokinetics of topiramate.
The mean pharmacokinetic parameters are summarized in the table below .

Parameters	Digoxin Alone	Digoxin with Topiramate
C_{max} (ng/mL)	5.82 ± 1.39	4.90 ± 1.08
T_{max} (h)	0.88 ± 0.39	0.79 ± 0.28
AUC (0-72 h) (ng*h/mL)	37.2 ± 7.1	33.9 ± 6.6
AUC (0-∞) (ng*h/mL)	49.6 ± 11.2	43.6 ± 10.2
t1/2 (h)	38.9 ± 6.8	36.0 ± 4.7
CL/F (mL/min)	214 ± 59	241 ± 54

Values are reported as Mean ± SD

COMMENTS:

It is recommended that initiation or termination of topiramate therapy in patients on digoxin therapy be made with careful attention, monitoring for digoxin serum concentrations so that adjustment in digoxin dosage may be made if necessary. Furthermore, this study does not describe the effect of digoxin on the pharmacokinetics of topiramate.

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STUDY TITLE #20: Pharmacokinetic/Pharmacodynamic Analysis: The Relationship of Steady-State Topiramate Plasma Concentration to Clinical Efficacy and Safety in Double-Blind, Placebo-Controlled, Adjunctive Therapy Trials (Protocols YD, YE, and Y3, December, 1994).

OBJECTIVES: The objective of this study was to compare the safety and efficacy of topiramate 200, 400, 600, 800, and 1000 mg/day doses administered twice a day in patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs. The evaluation of the relationship between steady-state plasma topiramate concentration and clinical safety and efficacy parameters is reported here.

FORMULATION: 100 mg Tablet Batch R4330, Formula No. 1,
100 mg Tablet Batch R4328, Formula No. 1, and
100 mg Tablet Batch R4371, Formula No. 1;
all manufactured at Spring House, PA.

STUDY DESIGN AND SAMPLING:

These studies were multicenter, outpatient, parallel, double-blind, randomized, placebo-controlled, adjunctive therapy clinical studies to compare the safety and efficacy of different topiramate doses in patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs. Following a baseline period, patients were randomly assigned to placebo or to a topiramate dose. Dose groups ranged from 200 to 1000 mg per day. Topiramate doses were titrated up to the assigned dose or to the maximum tolerated dose. Trough plasma samples (8-16 hrs postdose) were collected throughout the titration and stabilization periods of the study.

Percent reduction in seizure rate was defined as:

$$\text{Seizure rate} = 100\ (B\text{-}S)/B$$

Where B = baseline seizure rate and S= stabilization period seizure rate.
The average monthly seizure rate for a time period was calculated as the total number of seizures reported during the period divided by the number of days in the period multiplied by 28. The baseline seizure rate was calculated as the average monthly seizure rate for the pretreatment period (maximum of 12 weeks). The stabilization seizure rate was defined for each subject as the average monthly seizure rate over the portion of the stabilization period completed by that subject. The percent reduction in seizure rate was plotted against the mean trough plasma topiramate concentration. Kendall's correlation coefficients for these two variables were calculated for all subjects and for men and women separately.

Results:

No statistically significant correlation was observed between plasma concentration and percent reduction in seizure rate (Attachment 1). Though there was no consistent correlation between mean plasma topiramate concentration and percent reduction in average monthly seizure rate, the median percent reduction in seizure rate and increasing plasma concentration suggests a positive relationship between the reduction in seizure rate and increasing plasma concentrations up to the 3.4 - 5.2 µg/mL (Attachment 2 & 4). At plasma topiramate concentrations of 5.2 µg/mL or greater, a decrease from the peak seizure rate reduction was observed.

CONCLUSIONS:

Although most patients experienced a decrease from their baseline seizure rate due to topiramate therapy, there was no apparent correlation between percent reduction in seizure rate and plasma topiramate concentration. The data suggest that the median percent reduction in seizure rate increases with increasing plasma topiramate concentration and peaks at mid-range plasma topiramate concentration, of 3.4 - 5.2 µg/mL.

STUDY # 21: Population pharmacokinetics of topiramate from three double-blind, parallel, placebo-controlled, adjunctive therapy clinical studies (Protocols YD, YE, and Y3, January, 1994).

OBJECTIVES: This study was designed to evaluate the safety and efficacy of different doses of topiramate in patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs. The secondary objectives of this study were to develop a population pharmacokinetic model to evaluate (i) the effects of weight, age, gender, and race on clearance and volume (ii) the effects of other antiepileptics on clearance of topiramate.

FORMULATION: 100 mg Tablet Batch R4330, Formula No. 1;
100 mg Tablet Batch R4328, Formula No. 1, and
100 mg Tablet Batch R4371, Formula No. 1; all manufactured at McNeil Pharmaceutical, Spring House, PA.

STUDY DESIGN AND SAMPLING:

These three phase II studies (multicenter, outpatient, parallel, and randomized) were designed to evaluate the safety and efficacy of 200, 400, 600, 800, and 1000 mg daily doses of topiramate in two equally-divided doses compared with placebo as adjunctive therapy for 427 patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs (demographics and background of patients attached, Attachment 1) . The topiramate dose was titrated up to the assigned dose or to the maximum tolerated dose (increments were usually weekly). Plasma samples were collected from patients during titration and stabilization phases of the protocol. Data included in the analyses were restricted to the stabilization phase of the protocols and all plasma concentrations were assumed to be at steady state. The data base used in the analysis consisted of 265 patients (19% female and 11% nonwhite).

Population Modeling:

Based upon previous pharmacokinetic analysis of topiramate data, a one-compartment model with first order absorption was selected. A parameterization of this model with terms for clearance, volume and absorption rate constant was used. The bioavailability was assumed to be 1.0. Interindividual error terms were estimated for clearance, volume and absorption rate constant. Objective function was used to select the model when covariates (age, race and gender) were used. Gender and race were selected so that the underlying estimates were for white males. Both additive and mutiplicative error

models were used for population analysis and it was found that the multiplicative error model is superior based on minimum objective function (Attachment 2). Age was added to the model as an additive term, and weight, race and gender as multiplicative terms on clearance and volume. The effect of other antiepileptics (carbamazepine, phenytoin, valproic acid, phenobarbital, primidone and benzodiazepines) on topiramate clearance and volume were also evaluated.

Results:

Effects of weight, race, gender and race on clearance and volume:

The addition of weight on clearance did not reduce the objective function significantly (2045.6 for no weight effect vs 2044.5 for weight effect). The addition of weight on both clearance and volume produced a significant reduction in the objective function (2045.6 for no weight effect vs 2037.9 for weight effect). Based upon this reduction of objective function a model for both clearance and volume with weight as covariate was selected (Attachment 3).

There was no effect of gender, age and race on topiramate clearance (Attachment 4). Though there was no effect of age on topiramate volume, race and gender appeared to effect topiramate volume (Attachment 4); (according to the Sponsor, only gender appears to effect volume).

The equations for estimation of clearance and volume are as follows (as provided by the Sponsor):

Clearance (L/hr) = 3.49 + 0.0065 * wt (kg) ---------- (1)

Volume (L) (males) = -35.1 + 2.27 * wt (kg) ---------- (2)

Volume (L) (females) = 0.66 [-35.1 + 2.27 * wt (kg)] ---------- (3)

TABLE

Summary of model predicted estimates for Topiramate clearance and volume from NONMEM analysis (Sponsor's result)

Statistics	Clearance (L/hr)	Volume (L) Males	Volume (L) Females
Mean ± SD	4.02 ± 0.12	152.9 ± 36.5	83.4 ± 29.3
Range	3.74 - 4.41	70.0-284.4	34.7-171

Using the control stream provided by the Sponsor which included weight on both volume and clearance, a NONMEM run at the FDA gave identical objective function (2037.9) as described by the Sponsor. However, the parameters for clearance and volume

were different than that reported by the Sponsor. The following equations were obtained at the FDA:

Clearance (L/hr) = 6.71 + 0.0153 * wt (kg) ———————— (4)

Volume (L) = -126 + 5.02 * wt (kg) ———————— (5)

***Effects of antiepileptics on clearance:**

It is not possible to draw any conclusion from this study (please see comments). According to the Sponsor the antiepileptics (carbamazepine, phenytoin, valproic acid, phenobarbital, primidone and benzodiazepines) used in this study had no effect on topiramate clearance.

TABLE

Summary of model estimates for antiepileptic drug effect (Sponsor's result)

Statistics	Clearance (L/hr) -Topiramate Monotherapy	Clearance (L/hr) -Topiramate with other antiepileptics
Mean ± SD	2.97 ± 0.12	3.86 ± 0.46
Range	2.68 - 3.39	3.04 - 6.76

Conclusion:

In short, it appears that weight does have an effect on the clearance and volume of distribution of topiramate. Gender and race were identified as a covariates which influenced volume but not clearance. Age has no effect either on clearance or volume. No conclusion can be drawn from drug interaction study.

Comments:

The population pharmacokinetic study sponsored by R. W. Johnson has errors in the analysis which makes the interpretation of the results very difficult.

(i) The control stream provided by the Sponsor and run on NONMEM at the FDA, gave identical objective functiou but different parameter values. This may be due to different versions used by the Sponsor and the FDA.

(ii) The equation provided by the Sponsor for clearance is actually for volume not for clearance.

(iii) The Sponsor concludes that the race has no effect on volume. Inclusion of race on volume gives the lowest objective function i.e. race appears to have an affect on volume of topiramate.

Model	Objective Function
Weight only model	2037.9
Age on Volume	2036.5
Race on Volume	2033.3

(iv) For the drug interaction analysis, theta (3) has been skipped, whereas theta (11) has been used twice, for volume and absorption rate constant. Therefore, it is difficult to assess any conclusion from such a run.

In conclusion, it is difficult to assess the validity of the NONMEM analysis provided by the Sponsor.

Table 3: Demographic and Background Characteristics for Analyses

Characteristic	Protocols YD (n=120)	YE (n=121)	Y3 (n=25)	All Studies
Age (yrs)	Mean: 36.6 STD: 10.9 Range: 19-67	Mean: 35.7 STD: 11.4 Range: 18-67	Mean: 38.9 STD: 10.8 Range: 20-63	Mean: 36.4 STD: 11.1 Range: 18-67
Sex	Male: 94 Female: 26	Male: 100 Female: 21	Male: 22 Female: 3	Male: 216 Female: 50
Race	White: 105 Nonwhite: 15	White: 106 Nonwhite: 15	White: 25 Nonwhite: 0	White: 236 Nonwhite: 30
Daily Dose Received (mg) during Stabilization	100: 1 200: 42 300: 3 400: 40 500: 1 600: 33	100: 3 200: 3 300: 2 400: 11 500: 2 600: 35 800: 42 1000: 23	200: 1 300: 4 400: 4 500: 2 600: 2 800: 12	100: 4 200: 46 300: 9 400: 55 500: 5 600: 70 800: 54 1000: 23
Weight (kg)	Mean: 79.8[a] STD: 16.8 Range: 44-129	Mean: 82.3 STD: 18.9 Range: 39-141	Mean: 76.2 STD: 9.7 Range: 59-98	Mean: 80.6 STD: 17.3 Range: 39-141
Number of Patients Taking Concomitant Anti-epileptic[b]	Carba: 91 Pheny: 43 Valp: 34 Pheno: 15 Primi: 16 Benzo: 0	Carba: 89 Pheny: 40 Valp: 38 Pheno: 11 Primi: 14 Benzo: 0	Carba: 20 Pheny: 5 Valp: 2 Pheno: 3 Primi: 2 Benzo: 4	Carba: 200 Pheny: 88 Valp: 74 Pheno: 29 Primi: 32 Benzo: 4

a: Weight was not recorded for one patient (white male who received a 400 mg dose).
b: Carba.= Carbamazepine; Pheny.= Phenytoin; Valp.= Valproic Acid; Pheno.= Phenobarbital; Primi.= Primidone; Benzo.= Benzodiazepines.

There was a wide cross-section of concomitant antiepileptics used in the studies; approximately two-thirds of the patients received two antiepileptics in addition to topiramate.. Table 3 gives a breakdown of the distribution of the other antiepileptics among the patients.

Table 4: Summary of Parameter Estimates - Additive Vs. Multiplicative Error Model

Parameter	Additive Errors		Multiplicative Errors	
Objective Function	2256.099	2250.869	2045.599	2037.968
Intercept for Clearance (L/h)	3.87	3.35	4.04	3.36
Weight Effect on Clearance (L/h/kg)	fixed at 0	.00675	fixed at 0	0.00765
Intercept for Volume (L)	87.5	63.0	60.0	-63.0
Weight Effect on Volume (L/kg)	fixed at 0	0.380	fixed at 0	2.51
Absorption Rate (/h)	0.646	0.639	0.0293	1.01
Interindividual Error Variance for Clearance	1.18 (L/h)	1.20 (L/h)	0.104 ( )	0.0978 ( )
Interindividual Error Variance for Volume	8125 (L)	10400 (L)	8.16 ( )	1.04 ( )
Interindividual Error Variance for Absorption Rate	1.72 (/h)	1.86 (/h)	1.32 ( )	1.01 ( )
Intraindividual Error Variance	1.20 (mg/L)	1.21 (mg/L)	0.0503 ( )	0.0514 ( )

Residual analyses for the additive error models suggested that the absolute values of the weighted residuals increased with increasing predicted values. Given the much larger objective function values with an additive error model whether or not weight was in the model, it was decided to continue the analyses for other effects with a multiplicative error structure only.

Note that earlier residual analyses for the additive and multiplicative models identified one plasma concentration 38.298 µg/mL for protocol YE, investigator 34, patient 5 which was an extreme value for this and all other patients; this point was eliminated in the analyses above and all further analyses.

To examine the effects of weight on the basic pharmacokinetic model, the analyses of the basic model with multiplicative errors was repeated selectively fixing the slope coefficient for weight to zero for either the clearance or the volume. Results from these analyses are summarized in Table 5.

Table 5: Summary of Parameter Estimates - Effects of Weight on Models

Parameter	No weight effects	Weight effect for clearance	Weight effect for volume	Both weight effects
Objective Function	2045.599	2044.508	2040.768	2037.968
Intercept for Clearance (L/h)	4.04	3.76	4.02	3.36
Weight Effect on Clearance (L/h/kg)	fixed at 0	0.00317	fixed at 0	0.00765
Intercept for Volume (L)	60.0	3.60	-46.3	-63.0
Weight Effect on Volume (L/kg)	fixed at 0	fixed at 0	2.31	2.51
Absorption Rate (/h)	0.0293	0.0291	0.652	1.01
Interindividual Error Variance for Clearance ()	0.104	0.113	0.0949	0.0978
Interindividual Error Variance for Volume ()	8.16	0.0371	1.07	1.04
Interindividual Error Variance for Absorption Rate ()	1.32	1.32	7.44	1.01
Intraindividual Error Variance ()	0.0503	0.0519	0.0503	0.0515

Residual analyses of the multiplicative model without weight effects in the model did not strongly suggest that the addition of a weight effect for clearance or volume was needed. Based upon the estimates in the preceding table however, it is apparent that first adding a weight term for volume was more beneficial in obtaining a better fit to the data ($X^2_1 = 4.831$; p=0.027) than adding a weight term

Attachment 4.

Table 6: Effects of Adding Single Effects for Age, Sex, and Race

Model	Objective Function	Likelihood Ratio Criteria for added term
Weight only model	2037.968	----
Age Effect for Clearance	2035.756	2.212
Age Effect for Volume	2036.509	1.459
Sex Effect for Clearance	2037.966	0.002
Sex Effect for Volume	2033.976	3.992
Race Effect for Clearance	2037.901	0.067
Race Effect for Volume	2033.298	4.670

Table 7: Summary of Parameter Estimates and Standard Errors for Models with Race or Sex Effects for Volume

Model	Objective Function	Intercept for Clearance	Weight Effect for Clearance	Absorption Rate
Sex/~~Race~~ Effect should be	2033.976	3.36 (0.472)	0.0077 (0.0056)	1.00 (0.332)
Race/~~Sex~~ Effect for V	2033.298	3.49 (0.443)	0.00650 (0.00525)	1.00 (0.300)

Model	Intercept for Volume	Weight Effect for Volume	Race Effect for Volume	Sex Effect for Volume
Race Effect	-67.5 (39.2)	2.67 (0.83)	-0.188 (0.072)	NA
Sex Effect	-35.1 (34.5)	2.27 (0.69)	NA	-0.170 (0.110)

Model	Error Variance for Clearance	Error Variance for Volume	Error Variance for Absorption	Intraindividual Error Variance
Race Effect	0.0998 (0.0123)	1.04 (0.425)	0.729 (2.55)	0.0514 (0.00526)
Sex Effect	0.0924 (0.0121)	1.07 (0.540)	7.72 (1.88)	0.0498 (0.00516)

The models with weight effects for clearance and volume and either a race or sex effect for volume were then used as the basis to add another single age, sex, or race effect or to remove the effect of weight on clearance and volume (Table 8).

Table 8: Effects of Adding Single Age, Sex, and Race Effects or Removing Weight Effect from Model with Race Effect for Volume

Model	Objective Function	Likelihood Ratio Criteria
Weight Effects for Clearance and Volume, Race Effect for Volume	2033.298	----
Adding Age Effect for Clearance	2031.314	1.984
Adding Age Effect for Volume	2031.859	1.439
Adding Sex Effect for Clearance	2033.276	0.022
Adding Sex Effect for Volume	2031.519	1.779
Adding Race Effect for Clearance	2032.332	0.966
Removing Weight Effect for Clearance	2036.606	(3.308)
Removing Weight Effect for Volume	2042.888	(11.574) X 9.59

Since the reductions in the objective function (the Likelihood Ratio Criteria) are small, no additional improvement in the fit of model would be expected with the addition of another term to the model beyond this model with weight terms for both clearance and volume and a race term for volume. Since the increases in the objective function are relatively large when removing terms, no improvement in the fit of this model would be expected by removing either of the weight terms from the model.

Since only 11% of the patients in this analysis were nonwhite and there are few biological reasons to believe that there would be a race effect on the apparent

volume of distribution, this model is not considered entirely plausible. The model which does give an adjustment to the volume due to the sex of the patient is biologically plausible.

Table 9 summarizes the effect of adding or subtracting terms from the model with weight terms for both clearance and volume and a sex term for volume. Since the reductions in the objective function (the Likelihood Ratio Criteria) are small no additional improvement in the fit of model would be expected with the addition of another term to the model beyond this model. The only term that might be added is an effect of race on volume, but this is not statistically significant ($X^2_1 = 2.457$; p=0.117). Since the increases in the objective function are relatively large when terms are removed from the model, no improvement in the fit of this model would be expected by removing either of the weight terms from the model.

Table 9: Effects of Adding Single Age, Sex, and Race Effects or Removing Weight Effect from Model with Sex Effect on Volume

Model	Objective Function	Likelihood Ratio Criteria
Weight Effects for Clearance and Volume, Sex Effect for Volume	2033.976	----
Adding Age Effect for Clearance	2033.005	0.971
Adding Age Effect for Volume	2032.793	1.183
Adding Sex Effect for Clearance	2033.921	0.055
Adding Race Effect for Clearance	2033.628	0.348
Adding Race Effect for Volume	2031.519	2.457
Removing Weight Effect for Clearance	2039.611	(5.635)
Removing Weight Effect for Volume	2039.086	(6.081)

Table 11: Summary of Parameter Estimates and Standard Errors for Antiepileptics

Intercept for Clearance	Weight Effect for Clearance	Carbamazepine Effect for Clearance	Phenytoin Effect for Clearance	Valproic Acid Effect for Clearance
2.20 (0.60)	0.00915 (0.00489)	0.155 (0.121)	0.276 (0.149)	0.0595 (0.0605)

Phenobarbital Effect for Clearance	Primidone Effect for Clearance	Benzodiazepine Effect for Clearance	Intercept for Volume	Weight Effect for Volume
0.00985 (0.0920)	0.171 (0.119)	0.705 (0.319)	-68.0 (28.6)	2.50 (0.59)

Absorption Rate	Error Variance for Clearance	Error Variance for Volume	Error Variance for Absorption	Intraindividual Error Variance
0.702 (0.145)	0.0788 (0.0100)	1.12 (0.461)	4.66 (4.30)	0.0494 (0.00525)

From this model and the estimated asymptotic standard errors, it is anticipated that neither phenobarbital nor valproic acid are contributing substantially to the reduction in the objective function. The results of singularly removing each of the antiepileptics are summarized in Table 12.

Table 12: Effects of Removing One Antiepileptic from Model When All Are Present

Model	Objective Function	Likelihood Ratio Criteria
All Antiepileptics	1956.609	—
Removing Carbamazepine	1991.806	35.197
Removing Phenytoin	2013.584	56.975
Removing Valproic Acid	1960.513	3.904
Removing Phenobarbital	1956.880	0.271
Removing Primidone	1968.565	11.956
Removing Benzodiazepines	1975.198	18.589

From this table it is clear that removing the effect of phenobarbital should have little effect on the fit of the data ($X^2_1 = 0.271$; p=0.603). The results from removing the next antiepileptic are as follows (Table 13):

Table 13: Effects of Removing Second Antiepileptic from Model when all are present

Model	Objective Function	Likelihood Ratio Criteria for removing term
All Antiepileptics except Phenobarbital	1956.880	—
Removing Carbamazepine	1972.602	15.722
Removing Phenytoin	2019.123	62.243
Removing Valproic Acid	1960.539	3.659
Removing Primidone	1970.056	13.176
Removing Benzodiazepines	1975.205	18.325

From the above table it is not apparent that removing any other effect is needed. Valproic acid has the smallest change but it is almost statistically significant

(X^2_1 = 3.659; p=0.056) and would not be a very good candidate. The results of the parameter estimation with phenobarbital removed are in Table 14.

Table 14: Summary of Parameter Estimates and Standard Errors for Antiepileptics with Phenobarbital Removed

θ_1 Intercept for Clearance	θ_2 Weight Effect for Clearance	θ_4 Carbamazepine Effect for Clearance	θ_5 Phenytoin Effect for Clearance	θ_6 Valproic Acid Effect for Clearance
2.41 (0.432)	0.00695 (0.00383)	0.110 (0.071)	0.202 (0.082)	0.0430 (0.0387)

θ_7 Phenobarbital Effect for Clearance	θ_8 Primidone Effect for Clearance	θ_9 Benzodiazepine Effect for Clearance	Intercept for Volume	Weight Effect for Volume
fixed at 0	0.122 (0.068)	0.525 (0.192)	-67.5 (28.9)	2.50 (0.60)

Absorption Rate	Error Variance for Clearance	Error Variance for Volume	Error Variance for Absorption	Intraindividual Error Variance
0.705 (0.155)	0.0790 (0.00997)	1.12 (0.457)	4.53 (4.47)	0.0494 (0.00526)

Table SD6 contains a listing of the observed and predicted plasma concentrations from this model. Table SD7 contains a listing of the estimated values of clearance, volume and steady-state trough plasma concentration from the parameter estimates provided; Table 15 summarizes these parameters.

STUDY #22: Bioanalytical methods used for the analysis of topiramate in biological samples from clinical pharmacokinetic studies (March, 1993).

Introduction:

R. W. Johnson. The structure of topiramate (2, 3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate) and the internal standard (1,2:3, 4-bis-O-(1-methylethylidene)-β-D-galactopyranose sulfamate) are shown in the Appendix.

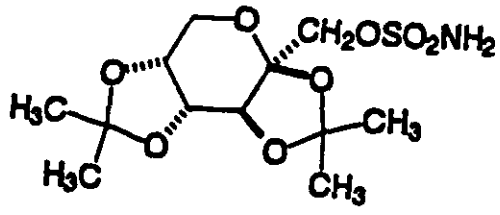
Sample preparation:

Plasma (0.1 mL) was extracted under acidic conditions into methyl t-butyl ether and the organic layer removed and back extracted with 0.2 M NaOH. Following acidification of aqueous solution, a further extraction into methyl t-butyl ether was performed. The organic layer was removed, evaporated to dryness, and redissolved in toluene/methanol. An aliquot of this solution was injected for GC-NPD analysis.

The standard curve for plasma ranged from 0.5-50 µg/mL with a 100 µl aliquot, whereas with 500 µl aliquot the range was from 0.1-10 µg/mL. Using 100 µl whole blood or urine the range was 0.5-50µg/mL in both the fluids. Limit of Quantitation (LOQ) of 0.1 µg/mL and 0.5 µg/mL were reported for plasma. LOQ values of 0.5 µg/mL were reported for whole blood, urine and dialysate fluid samples. Quality control samples were prepared for all the assays for topiramate in the appropriate biological matrix at the time of validation. Three or four concentrations were chosen at values close to the LOQ, intermediate concentrations and upper range of the standard curves. The accuracy was within 5% of theroretical concentrations and the precision of all topiramate assays was less than 10%. No interference was observed between topiramate and internal standard. The recovery of topiramate from plasma ranged from 68-100%, 92% from urine, 86% from whole blood and 78% from dialysate fluid. Assays for plasma confirmed room temperature stability for up to 4 days and for three freeze/thaw cycles. Assays for urine, whole blood and dialysate fluid confirmed room temperature stability for 3, 7, and 8 days, respectively, and for three freeze/thaw cycles. Long-term stability of topiramate in frozen biological samples was confirmed for upto 6 months for plasma and urine.

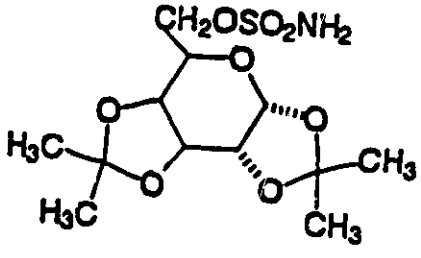
Figure SD1: Structures of (A) Topiramate (RWJ-17021-000) and the Internal Standard (B) RWJ-35482-000

A. Topiramate (RWJ-17021-000): 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate



M.W.= 339.36

B. RWJ-35482-000: 1,2:3,4-bis-*O*-(1-methylethylidene)-β-D-galactopyranose sulfamate



M.W.= 339.36

2 Pages
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DISSOLUTION

5 Pages

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PROTEIN BINDING

range (Protocol MS-210).[7] The mean total body plasma clearance values of topiramate following 50, 100, and 200 mg q24h dosing regimens for 14 days were 28.5 (3.4), 30.8 (7.0), and 31.6 (4.1) mL/min, respectively. With 50 and 100 mg q12h dosing regimens for 14 days, the plasma clearance values were 27.5 (6.4) and 31.0 (7.9) mL/min, respectively (Protocol YB).[6] The mean renal clearance of topiramate was 13.92 mL/min across a 100-1200 mg single oral dose range (Protocol YA).[8] The mechanisms of renal elimination of topiramate may involve significant tubular reabsorption in the kidney. This is supported by studies in rats where a significant increase in the renal clearance of topiramate was observed due to coadministration with probenecid, suggesting reabsorption of topiramate in the kidney by a carrier-mediated process. The mean renal clearance values of topiramate following 50, 100, and 200 mg q24h dosing regimens for 14 days were 19.1 (2.9), 18.1 (7.1), and 17.5 (3.2) mL/min, respectively. The mean renal clearance values for the 50 and 100 mg q12h dosing regimens were 17.8 (6.6) and 16.7 (6.5) mL/min, respectively (Protocol YB).[6]

4. Protein Binding

The in vitro binding of topiramate to plasma proteins and to erythrocytes of mouse, rat, rabbit, dog, monkey, and human was studied using radiotracer methodology and microequilibrium dialysis techniques.[26] ^{14}C-topiramate (40 µCi/mg, Lot No. 5040-90) proved to be stable under the incubation conditions employed in these experiments. The drug was poorly bound to plasma proteins of all species studied. Generally between 9% and 17% of added topiramate (1-250 µg/mL, final concentration) was bound to plasma proteins. The clinically relevant topiramate plasma concentration range has been found to extend as high as 33 µg/mL. An exception was monkey plasma which bound 6% or less of added topiramate at

concentrations greater than 40 µg/mL. Saturation of plasma protein binding sites was evident in samples obtained from mouse, monkey and man. In addition, there appeared to be a high affinity, low capacity binding site for topiramate in the erythrocytes of all species studied. Binding constants for this site in rat and dog blood were determined. The dissociation constant for the high affinity site in dog erythrocytes (0.27 µg/mL, 0.80 µM) was slightly lower than that in rat erythrocytes (0.38 µg/mL, 1.12 µM). The binding capacity of this site for topiramate was twice as large in the rat (21.83 µg/mL) as in the dog (10.80 µg/mL) erythrocytes.

E. EXTERNAL FACTORS WHICH MAY INFLUENCE PHARMACOKINETICS

1. Renal Impairment (Protocol MS-191A)[10]

The objective of this study was to determine the pharmacokinetics and renal excretion of topiramate in 18 renally impaired subjects as compared to 18 subjects with normal renal function following oral administration of one 100 mg topiramate tablet (Formula No. 1, Batch No. R4504). The subjects with normal renal function were matched to the subjects with renal impairment by age (±10 years), gender, and weight (±20 pounds).

Statistical analysis was conducted for 28 of the subjects by comparison of pharmacokinetic parameters from 14 renally impaired subjects vs. those from 14 matched subjects with normal renal function. The paired subjects included two groups of seven each with CL_{CR} less than 30 mL/min/1.73M^2 and 30 to 69 mL/min/1.73M^2, respectively, who were each matched with subjects having CL_{CR} equal to or greater than 70 mL/min/1.73M^2.

In-Vitro Human Liver Microsomal Studies

Table 63: Duration of Ethanol-Induced Narcosis
Preclinical Ethanol Interaction Study[24]
Mean ±SD

Treatment	Number of rats	Duration (min)
Topiramate alone	5	0 ± 0
Topiramate + ethanol	4	89 ± 32
Ethanol alone	5	26 ± 40

The duration of ethanol-induced narcosis was significantly longer (242%) for the topiramate plus ethanol group than for the ethanol alone group ($p<0.05$).

Interaction between topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Based on the results of the preclinical study, it is recommended that topiramate should not be used concomitantly with alcohol or other CNS depressant drugs.

8. Human Liver Microsomes[23]

In vitro human liver microsomal incubations were used to investigate the effects of topiramate on the isoforms of cytochrome P450 which are responsible for oxidative drug metabolism in the human.[23] Varying concentrations of topiramate (0.5 µM-1 mM) were incubated with noninduced human liver microsomes and compounds for which certain metabolic pathways have been demonstrated to be specifically catalyzed by single isoforms of cytochrome P450. The substrates used were incubated at concentrations close to the K_m for the specific pathways being studied. The specific reactions studied were 6-, 7-, and 8-hydroxylation of R-warfarin, 7-hydroxylation of coumarin, the 7-hydroxylation of S-warfarin, the 4'-hydroxylation of S-mephenytoin, the 1"-hydroxylation of bufuralol,

catechol formation from *p*-nitrophenol, and 10-hydroxylation of R-warfarin which are specific markers for the 1A2, 2A6, 2C9, $2C_{meph}$, 2D6, 2E1, and 3A3/4 isoforms of cytochrome P450, respectively. The results are shown in Table 64.

Table 64: Results of In Vitro Human Liver Microsomal Studies[23]

Human P450 Isoform	Substrates	Inhibition	Prediction
CYP1A2	R-Warfarin	No	No interaction with caffeine, theophylline
CYP2A6	Coumarin	No	No interaction with coumarin
CYP2C9	S-Warfarin	No	No interaction with phenytoin involving this isoform
$CYP2C_{meph}$	1'R-bufuralol[a] mephenytoin	Yes	Potential interaction with phenytoin
CYP2D6	1'R-bufuralol 1'S-bufuralol	No No	No interaction with metoprolol, timolol, bufuralol, sparteine, propafenone, flecainide, nortriptyline, desipramine, clomipramine, perphenazine, thioridazine, debrisoquine, 4-hydroxyamphetamine, phenformin, amiflamine, perhexiline, dextromethorphan, indoramin, methoxyphenamine, codeine, encainide, imipramine, amitriptyline
CYP2E1	*p*-nitrophenol	No	No interaction with chlorzoxazone, disulfiram, enflurane, halothane, sevoflurane, methoxyflurane
CYP3A3/4	R-Warfarin	No	No interaction with carbamazepine, cyclosporin, midazolam, triazolam, levostatin, digitoxin, tamoxifen, dapsone, nifedipine, erythromycin, azithromycin, lidocaine, quinidine, acetylenic steroids, ergot alkaloids, benzphetamine, testosterone, cortisol, ethyl morphine

[a] In a CYP2D6-deficient microsomal preparation

Incubations of ^{14}C-topiramate (20 or 200 μM) were also carried out in human liver microsomes. No metabolites were detected by TLC in any of the incubations.

G. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS[21]

Three multicenter, outpatient, parallel, double-blind, randomized, placebo-controlled, adjunctive therapy clinical studies, Protocols YD, YE, and Y3, were conducted to evaluate the comparative efficacy and safety of topiramate in patients with refractory partial epilepsy on a maximum of two concomitant antiepileptic drugs. In addition, the relationship between steady-state topiramate plasma concentration and clinical efficacy and safety was evaluated in these studies.[21] In each study, following a 12-week (Protocols YD and YE) or 8-week baseline period (Protocol Y3), patients were randomly assigned to placebo or to a topiramate dose. Topiramate dose groups were 200, 400, and 600 mg per day for Protocol YD; 600, 800, and 1000 mg per day for Protocol YE; and 800 mg per day for Protocol Y3. The topiramate dose was titrated up (usually in weekly increments) to the assigned dose or the maximum tolerated dose. Patients continued to be followed in a double-blind fashion for an additional 12 weeks (Protocols YD and YE) or 8 weeks (Protocol Y3) (stabilization period) on this regimen. Patients then entered an open extension or were tapered off topiramate.

Topiramate 100 mg tablets (Formula No. 1/Batch No. R4330, Protocols YD/YE; Formula No. 1/Batch No. R4328, Protocol YD/Y3; and Formula No. 1/Batch No. R4371, Protocol YD) were used in these studies.

Dosage Form

4 Pages
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