# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 020844

## MEDICAL REVIEW(S)

**MEMORANDUM**

DATE: June 26, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-844

SUBJECT: Supervisory Review of NDA 20-844, Topamax Sprinkles

R.W. Johnson Pharmaceutical Research Institute submitted NDA 20-844, for Topamax Sprinkles, (15, 25, and 50 mg strengths) on 8/18/97. Topamax is an anti-seizure drug approved on 12/24/97as adjunctive treatment for adults with partial seizures. The sponsor wishes to have available a sprinkle formulation for those patients who have difficulty swallowing (on the same date, the sponsor submitted several NDA supplements, which include data to support the extension of various claims to pediatric patients).

This NDA consists of reports of 3 bioequivalence studies and 2 studies designed to evaluate the palatability and patient acceptability of this dosage form. In addition, relevant CMC and dissolution data have been submitted. The bioequivalence and dissolution data have been reviewed by Dr. Iftekhar Mahmood (review dated 6/3/98), the clinical safety and palatability data have been reviewed by Dr. Richard Tresley (review dated 5/9/98), and the CMC data have been reviewed by Dr. Mona Zarifa (reviews dated 6/8/98 and 6/15/98). In this memo, I will briefly review the relevant data, and offer my recommendations for action on the NDA.

**BIOEQUIVALENCE**

Of the 3 bioequivalence studies submitted, 2 were considered of probative value (the third was a pilot study designed to assess the performance of several early versions of the product).

**STUDY TOPMAT-PHI-359**

This was a single dose, open label, counterbalanced cross-over study in healthy volunteers in which the performance of the marketed 100 mg tablet was compared to that of the contents of two 50 mg sprinkle capsules sprinkled onto 2 tablespoons of applesauce in the fasted state. There was a 3 week washout between treatments, and blood was sampled for 72 hours after dosing.

A total of 18 subjects were enrolled, with 16 being included in the PK analysis.

There were no statistically significant differences between formulations for Cmax, AUC, tmax, t1/2, CL/F, or ke. Formal comparisons of Cmax and AUC met usual standards for bioequivalence (2, one sided confidence interval approach).

**STUDY TOPMAT-PHI-360**

This was a single dose, open label, three period cross-over study in healthy volunteers designed to compare the performance of two 50 mg sprinkle tablets given in applesauce in the fasted (Treatment A)and fed (Treatment B) state and two 50 mg capsules given intact in the fasted state (Treatment C). There was a three week washout between treatments, and blood was sampled for 72 hours after dosing in each period.

A total of 24 subjects were enrolled, with 20 being included in the PK analysis.

Comparisons of PK parameters between Treatments A and B and Treatments A and C revealed no statistically significant differences except for tmax (the tmax for Treatment A-3.7 hours-was 24 % and 46% greater than that of Treatments B and C, respectively). Comparisons of Cmax and AUC met standard equivalence criteria (comparisons of tmax were not made).

**SAFETY/PALATABILITY/ACCEPTABILITY**

There were no safety concerns of note. The sprinkle formulation was determined to be acceptable (as a substitute for marketed topiramate, determined in 15 pediatric patients) and palatable (as judged by 48 healthy volunteers).

**COMMENTS**

The sponsor has submitted appropriate bioequivalence studies which demonstrate the bioequivalence of the 50 mg sprinkle capsule to the marketed tablet. They have requested a waiver of the requirement for equivalence studies for the lower strengths of the sprinkle capsule, and, based on dose proportionality and dissolution data, Dr. Mahmood concludes that the waiver should be granted. In addition, Dr. Mahmood requests that the sponsor adopt particular dissolution specifications.

Dr. Zarifa has several comments to which the sponsor must respond prior to approval, as does the Nomenclature Committee.

**RECOMMENDATION**

The sponsor should be sent the attached Approvable letter with the attached draft labeling.

/S/

Russell Katz, M.D.

cc:
NDA 20-844
HFD-120
HFD-120/Katz/Leber/Ware

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

# CLINICAL REVIEW OF NDA

| | |
|---|---|
| NDA Number | 20,844 |
| Generic (Brand) Name | Topamax (topiramate) |
| Sponsor | RW Johnson Pharmaceutical Research Institute |
| Indication | Sprinkle Capsules |
| Classification | S |
| Correspondence Date | 18 August 1997 |
| Original Receipt Date | 19 August 1997 |
| Clinical Reviewer | Richard M. Tresley, MD |
| Review Completed | 9 May 1998 |

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# I. INTRODUCTION

Topamax (TOP) was approved as adjunctive therapy to treat partial seizures in adults with epilepsy on December 24, 1997. The sponsor has recently submitted three supplemental NDAs to support indications for use, as an adjunctive agent, in the treatment of (1) pediatric partial-onset seizures, (2) Lennox-Gastaut syndrome, and (3) primary generalized tonic-clonic seizures with or without other generalized seizure subtypes.

The sponsor has also submitted a new NDA to support the indication of sprinkle capsules for patients who have difficulty swallowing tablets. Three strengths are planned, 15, 25, and 50 mg. The present submission consists of five studies:

(1) an open-label, randomized, three-way crossover bioavailability study (TOPMAT-PHI-357) in 9 normal, healthy subjects, comparing sprinkle formulations to a 100-mg market-image tablet;

(2) an open-label, randomized, two-way crossover bioequivalence study (TOPMAT-PHI-359 in 18 normal, healthy subjects, comparing an sprinkle formulation to a 100-mg market-image tablet;

(3) an open-label study in 24 normal, healthy subjects, evaluating the effect of food on the pharmacokinetics of sprinkle formulation;

(4) a randomized, double-blind, taste-acceptability study in 48 normal, healthy males (aged ), comparing the sprinkle formulation;

(5) a randomized, open-label palatability study in 15 male and female pediatric subjects (aged 3-14) with epilepsy, assessing the taste of 25- and 50-mg sprinkle tablets.

Safety information has been provided for review. There were no deaths or serious adverse events in any of the studies.

According to current labeling, TOP exhibits rapid absorption: peak plasma concentrations occur at about 2 hours following a 400-mg oral dose. The relative bioavailability of the tablet formulation, compared to a solution, is about 80% and is not affected by food.

Pharmacokinetics are linear, with dose-proportional increases in plasma concentration over the 200 to 800 mg/day dose range. The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is reached in about 4 days in patients with normal renal function. TOP is bound to human plasma proteins over the concentration range of ug/ml.

TOP is not extensively metabolized and primarily eliminated unchanged in the urine (about 70% of an administered dose). Six metabolites -- formed by hydroxylation, hydrolysis, and glucuronidation -- have been identified in humans, none of which constitutes >5% of an administered dose. Animal studies have shown evidence of renal tubular reabsorption of TOP, but this interaction has not been evaluated in humans. Overall, plasma clearance in humans is about 20-30 ml/min after oral administration.

TOP's clearance was reduced by 42% in subjects with moderate renal impairment (creatinine clearance ml/min/1.73 m2), compared to normals (>70 ml/min/1.73 $m^2$). The clearance may also be decreased in subjects with hepatic impairment. Clearance was not affected by age, gender, or race. TOP's pharmacokinetics were assessed in patients, aged , receiving 1-2 other antiepileptic drugs (AEDs) at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose, but weight-adjusted clearance may be higher in pediatric than adult patients.

Dr. Iftekar Mahmood (FDA Biopharm) has reviewed the sponsor's submission. The sponsor's proposed dissolution specification is Q = at seconds, but the FDA has requested that the company raise its standard to Q = at seconds. Dr. Mahmood recommends the following labeling changes as well:

(a) Under "Pediatric Pharmacokinetics," add the phrase

(b) Under "Oral Contraceptive Pharmacokinetics," add the phrase "The oral clearance of ethinyl estradiol at an 800 mg/day total dose was increased by 47% "

## II. TOPMAT-PHI-357

This was a single-center open-label, randomized, three-way crossover study, conducted 7/27/95-9/11/95, to assess the comparative bioavailability of TOP from single-dose sprinkle formulations relative to a 100-mg market-image tablet formulation. Nine normal, healthy males (aged 18-40) were enrolled in three treatment periods (inclusion/exclusion criteria were standard; see Table 2 for demographic breakdown) in random sequence:

*Treatment A* administered a single 100-mg market image tablet following the ingestion of two tablespoons (30 ml) applesauce.

*Treatment B* contained a 100-mg dose of TOP as two 50-mg capsules of sprinkle formulation mixed with two tablespoons applesauce.

*Treatment C* contained a 100-mg dose of TOP as two 50-mg capsules of sprinkle formulation mixed with two tablespoons applesauce.

Blood samples were collected for 72 hours following the TOP dose and analyzed for TOP concentration by After a washout period of at least three weeks, the subjects were crossed over to the alternate treatments in Periods 2 and 3.

All enrolled subjects completed the trial as outlined in the protocol and were included in the safety base. One subject (#109) was excluded from the pharmacokinetic data analysis because no plasma concentrations for the third dosing period were found, suggesting noncompliance.

Table 3 displays the pharmacokinetic results. There was a slight trend toward decreased AUC with higher bead coating, indicating decreased TOP absorption. AUC, $C_{max}$, and $T_{max}$ were comparable for the three formulations. The half-life of the sprinkle formulation was 4 hours less than the sprinkle and 100-mg market-image formulations.

Safety results showed that three subjects experienced seven adverse events; see Table 4. Headache was the most frequent complaint (two reports in one subject after both the 100-mg tablet and sprinkle formulation, and one each in the other two subjects after the sprinkle formulations), and occurred following all thee treatments. The subject who reported a headache after the sprinkle formulation had also, on the same day as his headache, registered the other three complaints (pallor, dizziness, and nausea). All adverse events were of "mild severity," resolving spontaneously within 24 hours, and evaluated by the investigator as "unlikely to be related to study drug." There were no deaths, serious adverse events, or significant abnormalities in laboratory values, exam, or vitals.

The sponsor concluded that both the sprinkle formulations were "likely to be bioequivalent to the TOP reference tablet."

## III. TOPMAT-PHI-358

This was a single-center, randomized, double-blind study, conducted 9/11/95-9/30/95, to assess the ability of each of three coating percentages (

48 normal, healthy males (inclusion/exclusion criteria were standard; see Table 2 for demographic breakdown), aged 18-55, who demonstrated sensory recognition of bitter taste, were randomly assigned to one of six possible treatment sequence groups. Every subject sequentially sampled each of the three coated-bead formulations, by first tasting a bitter standard solution consisting of 0.05% caffeine and then one of the three coated-bead formulations; 20 minute intervals separated each taste test. Subjects were asked to evaluate the taste acceptability of each formulation, to compare the bitterness intensity of each formulation with the caffeine solution, and to assess the overall taste acceptability of each coated-bead formulation in terms of willingness to repeat the study drug twice daily to treat a

serious, chronic illness.

Following were the criteria for evaluation:

(a) taste acceptability ratings: assessed at 30 and 60 seconds, on a 9-point scale of -4 (extremely unacceptable) to 4 (extremely acceptable) with 0 being neutral;

(b) bitterness intensity score: assessed at 30 and 60 seconds, on a magnitude scale in comparison to the standard caffeine solution, with the standard rated as 100; and

(c) overall taste acceptability: subject willingness to take the product as a medicine for a serious illness, based on a yes/no answer and assessed at the end of 60 seconds.

Means and standard deviations were calculated for taste acceptability ratings and bitterness intensity ratings. The effects of percentage coating on the taste acceptability and bitterness intensity ratings were analyzed by random effects models.

Mean acceptability scores ranged from formulation at seconds to formulation at seconds. These mean taste acceptability scores represent a rating between 0 and -1 (slightly unacceptable). Pair-wise comparisons of the three coatings showed statistically significant differences in acceptability rating for the coatings at both the -second assessments, and for the coatings at the second assessment ($p \leq 0.05$) by random effects modelling. The formulations did not differ significantly in their ability to mask TOP's taste (see Table 3).

Taste acceptability increased with the percentage. 29% of the subjects considered the formulation to be acceptable, and 56% the formulation, at the 60-second assessment (see Table 4).

Mean bitterness intensity scores at the 60-second assessment were 204 for the 13% formulation, 214 for the , and 246 for the Each of the three values reflected a bitterness intensity that was at least twice that of the standard caffeine solution (see Table 5).

73% of the respondents stated that they would take the formulation twice daily to treat a serious illness, compared to 87% for the and 82% for the formulations.

Study drug was expelled 60 seconds after tasting. Safety evaluations included three reports (6% of 48 subjects): one subject had mild asthenia (resolving spontaneously in one day), and two had mild headaches (one resolved spontaneously in one day, the other in five days). Vitals remained essentially unchanged.

## IV. TOPMAT-PHI-359

This was an open-label, randomized, two-way crossover study, conducted 2/29/96-4/11/96, to compare TOP's bioavailability from a 100-mg market-image tablet with a 100-mg sprinkle formulation administered as the contents of two 50 mg capsules mixed with two tablespoons of applesauce. Each treatment was given after an overnight fast, with a minimum three-week washout period between treatments. Following each treatment, blood samples were collected at protocol-specified time points for 72 hours. 18 normal, healthy males and females (inclusion/exclusion criteria were standard; see Tables 2.1 and 2.2 for demographics ), aged 18-40, were enrolled. Pharmacokinetic results were based on data from 16 participants. There were two dropouts (see Table 3): one due to anemia and abnormal erythrocytes (unlikely secondary to TOP, since both were low prior to study drug administration; see the narrative attached to Table 3) and the second for reasons listed as "other."

Table 4 and Figure 1 present the human PK data. There were no statistically significant differences between the two formulations when comparing ln-transformed pharmacokinetic parameters without normalizing for treatment formulation potency. There were also no statistically significant differences between the two formulations when comparing ranked $t_{max}$, raw $t_{max}$, and

$k_a$ (see Tables 5.1, 5.2, and 6).

The percent difference between the mean values of the pharmacokinetic parameters for the two treatments was less than 6%, except for $t_{max}$ (17.5%). Results of ANOVA indicated that there were no statistically significant differences between treatments for any of the PK parameters. Results before and after normalizing for treatment formulation potency gave confidence interval bounds for $C_{max}$, $AUC_{0-*}$, and $AUC_{0-inf}$ that were within the accepted bioequivalence interval

8/16 (50%) of the participants who took the 100-mg tablet, compared to 7/18 (39%) of those who the sprinkle, experienced treatment-emergent adverse events. The most common for both formulations were dizziness, paresthesia, and headache (see Table 7); in addition, 25% of those who took the tablet reported hypoesthesia. "Most. . .were of mild severity and considered to be possibly related to TOP" (v 9/15, p 37). The case of abnormal erythrocytes and anemia was felt to be of marked severity but unlikely to be related to study drug. There were no other treatment-related clinically significant lab abnormalities, changes in vitals, or exam findings. No deaths or serious adverse events were reported.

## V. TOPMAT-PHI-360

This was an open-label, randomized, three-way crossover study, conducted 4/1/96-7/12/96, to measure the effect of food and fasted state on the bioavailability of TOP from a single 100-mg oral dose of the formulation administered in applesauce. 24 normal, healthy males and females, aged 18-40 (inclusion/exclusion criteria were standard; see Table 2 for demographic breakdown), each underwent the following three treatments (randomly ordered in one of six possible sequences):

*Treatment A:* 100-mg TOP sprinkle formulation in applesauce in the fasted state (after a 10-hour fast)

*Treatment B:* 100-mg TOP sprinkle formulation in applesauce in the fed state (a standard breakfast eaten over 15 minutes, approximately 30 minutes prior to study drug administration)

*Treatment C:* 100-mg TOP sprinkle formulation in a capsule in a fasted state.

A three-week washout separated the treatments. Although 24 subjects were enrolled and participated in the safety analysis, only 20 were included in the PK analyses. Four subjects withdrew prematurely for reasons given in Table 3. Eight subjects had to be restarted in the study due to an error in the period 1 fed treatment.

The percent difference of the mean PK parameter values for the applesauce/fed and the capsule/fasted treatments from the applesauce/fasted treatment was less than 4.5%, except for $t_{max}$ (45.9%); see Table 4 and Figure 1. Results of ANOVA indicated that there were no statistically significant differences between treatments for any of the PK parameters (see Table 5.1 and 5.2); statistical significance was not seen for *ranked* $t_{max}$. The time to maximum concentration was longer for the applesauce/fed treatment than the other two treatments. Results from the two one-sided tests gave confidence interval bounds -- relative to the applesauce/fasted treatment -- for $C_{max}$, $AUC_{0-*}$, and $AUC_{0-inf}$ that fell within the guidelines for bioequivalence ; see Tables 6.1 and 6.2.

9/24 (38%) experienced treatment-emergent adverse events which resolved during the treatment period in which they were reported. Table 7 shows the most frequent as dizziness (25%) and headache (13%). Adverse events were similar to those found in current labeling. No treatment-emergent or clinically significant changes were reported on exams, vitals (prior to, during, and 72 hours after testing), or lab tests.

## VI. TOPIRAMATE SPRINKLE PALATABILITY STUDY (RWJ-17021)

Based upon the results in the taste acceptability study in adults, the formulation was chosen for further development. A study was consequently designed to confirm palatability of the sprinkle formulation in pediatric subjects. This was an open-label, two-center study, conducted 5/20/96-7/31/96 and involving 15 pediatric subjects (aged 3-14; ≥14 kg). All subjects were already receiving TOP tablets as part of their enrollment in the extensions for trials YP and EPPD-001, both studies for pediatric partial-onset seizures (see my review of the sNDA for study YP for inclusion/exclusion criteria; Table 2 shows the demographic breakdown). TOP sprinkle formulation replaced the morning tablet dose once daily for 3 days.

Study drug was mixed with about one tablespoon of soft food, such as applesauce, and administered in the investigator's office on day 1 and in the child's home on days 2 and 3. If the food was spit out or vomited, the subject was to be given the normal dose in regular tablet form. On days 1, 2, and 3, parents recorded whether the child spit out the sprinkle. On day 3, subjects completed a pictogram showing their reaction to the tablet and the sprinkle, and parents completed an overall assessment.

Criteria for evaluation centered on subject assessments of palatability based on responses to the questions, "How do you like TOP (white pills)?" and "How do you like TOP sprinkle?" A scale of 1 (excellent) to 7 (terrible) was used to score responses. A parental evaluation was also submitted and scored on (a) ease of use of TOP sprinkle, rated as either easy or hard, and (b) overall assessment of TOP sprinkle compared with TOP tablets rated as better, the same, or worse. Results were summarized in frequency tables for both subject and parent assessments.

With respect to palatability, 12 subjects rated the tablet as average or better. None of them spit out either the sprinkle or tablet during the study. In their overall assessment of the sprinkle formulation, 7 parents considered the sprinkle worse than the tablet, 5 the same, and 2 better. One parent failed to complete the evaluation. See Table 3, 4, and 5 for data displays.

Safety data included adverse events, vitals signs, exams, and clinical laboratory tests and "were reported as part of the open-label extension studies." The present NDA includes no safety data for this study; see my safety review of the sNDA for YP and EPPD-001.

# VII. CONCLUSION

TOP sprinkle formulation is bioequivalent to the tablet. The sponsor proposes three dosage strengths for TOP sprinkle: 15, 25, and 50 mg. There were no additional safety concerns not already in current labeling for the tablet form.

# VIII. RECOMMENDATION

I recommend approval of topiramate sprinkle formulation. The concerns of Dr. Mahmood (FDA Biopharm) should be reflected in the revised labeling:

(1) the dissolution specification , should be Q = at seconds;

(2) under the section "Pediatric Pharmacokinetics," the phrase

(3) under the section "Oral Contraceptive Pharmacokinetics," the phrase

should be added.

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,844 Supplements (Topamax sprinkle capsules) div file/Katz R/Ware J/Tresley R/9 May 1998

## IX. TABLES


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# CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

**Table 2:** Demographic and Baseline Characteristics
(All Subjects; Protocol TOPMAT-PHI-358)

| Characteristic | All Subjects (N = 48) | |
|---|---|---|
| **Sex** | | |
| Men | 48 | (100%) |
| **Age (years)** | | |
| Mean (SD) | 28.7 | (9.18) |
| Median | 25.5 | |
| Range (min-max) | 18 - 54 | |
| **Race** | | |
| White | 47 | (98%) |
| Other[a] | 1 | (2%) |
| **Weight (kg)** | | |
| Mean | 74.5 | (10.54) |
| Median | 74.4 | |
| Range | 54 - 100 | |

[a] Other = Oriental

**Table 3:** Mean Taste Acceptability Scores
(All Subjects; Protocol TOPMAT-PHI-358)

| Coating (% by Weight) | 30 sec. Mean | (SD) | Range (min-max) | 60 sec. Mean | (SD) | Range (min-max) |
|---|---|---|---|---|---|---|
| % | -0.27 | (1.95) | | -0.29 | (1.93) | |

**Table 4:** Summary of Taste Acceptability Ratings
(All Subjects; Protocol TOPMAT-PHI-358)

| Coating (% by Weight) | 30 sec. Un-acceptable No. | (%) | Neutral - Acceptable No. | (%) | 60 sec. Un-acceptable No. | (%) | Neutral - Acceptable No. | (%) |
|---|---|---|---|---|---|---|---|---|
| % | 25 | (52) | 23 | (48) | 26 | (54) | 22 | (46) |

**Table 5:** Mean Bitterness Intensity Scores
(All Subjects; Protocol TOPMAT-PHI-358)

| Coating (% by Weight) | 30 sec. Mean | (SD) | Range (min-max) | 60 sec. Mean | (SD) | Range (min-max) |
|---|---|---|---|---|---|---|
| % | 191 | (154.5) | | 214 | (192.4) | |





**Table 2.1:** Demographic and Baseline Characteristics
(All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-359)

| | | Treatment Sequence: Market-Image/ Sprinkle (N=9) | Sprinkle/ Market-Image (N=9) | Total (N=18) |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 31.6 (7.23) | 33.8 (4.89) | 32.7 (6.10) |
| | Median | 33 | 33 | 33 |
| | Range | (22.0,40.0) | (28.0,40.0) | (22.0,40.0) |
| Sex | Male | 4 ( 44%) | 4 ( 44%) | 8 ( 44%) |
| | Female | 5 ( 56%) | 5 ( 56%) | 10 ( 56%) |
| Race | White | 0 | 1 ( 11%) | 1 ( 6%) |
| | Black | 1 ( 11%) | 0 | 1 ( 6%) |
| | Asian | 0 | 0 | 0 |
| | Hispanic | 8 ( 89%) | 8 ( 89%) | 16 ( 89%) |
| Height (cm) | Mean (SD) | 165.7 (9.49) | 162.1 (5.76) | 163.9 (7.83) |
| | Median | 165.1 | 162.6 | 163.9 |
| | Range | (152.4,177.8) | (152.4,170.2) | (152.4,177.8) |
| Weight (kg) | Mean (SD) | 65.2 (8.45) | 67.3 (8.53) | 66.2 (8.30) |
| | Median | 65.8 | 66.7 | 66.7 |
| | Range | (53.1,77.6) | (51.8,78.0) | (51.8,78.0) |
| Frame | Small | 3 ( 33%) | 4 ( 44%) | 7 ( 39%) |
| | Medium | 6 ( 67%) | 5 ( 56%) | 11 ( 61%) |

**Table 2.2:** Demographic and Baseline Characteristics
(All Subjects Who Completed the Pharmacokinetic Evaluation; Protocol TOPMAT-PHI-359)

| | | Treatment Sequence: Market-Image/ Sprinkle (N=9) | Sprinkle/ Market-Image (N=7)[a] | Total (N=16) |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 31.6 (7.23) | 33.1 (4.95) | 32.3 (6.19) |
| | Median | 33 | 33 | 33 |
| | Range | (22.0,40.0) | (28.0,39.0) | (22.0,40.0) |
| Sex | Male | 4 ( 44%) | 4 ( 57%) | 8 ( 50%) |
| | Female | 5 ( 56%) | 3 ( 43%) | 8 ( 50%) |
| Race | White | 0 | 0 | 0 |
| | Black | 1 ( 11%) | 0 | 1 ( 6%) |
| | Asian | 0 | 0 | 0 |
| | Other[b] | 8 ( 89%) | 7 ( 100%) | 15 (94%) |
| Height (cm) | Mean (SD) | 165.7 (9.49) | 162.0 (6.48) | 164.1 (8.27) |
| | Median | 165.1 | 162.6 | 163.9 |
| | Range | (152.4,177.8) | (152.4,170.2) | (152.4,177.8) |
| Weight (kg) | Mean (SD) | 65.2 (8.45) | 67.7 (9.67) | 66.3 (8.78) |
| | Median | 65.8 | 66.7 | 66.7 |
| | Range | (53.1,77.6) | (51.8,78.0) | (51.8,78.0) |
| Frame | Small | 3 ( 33%) | 3 ( 43%) | 6 ( 38%) |
| | Medium | 6 ( 67%) | 4 ( 57%) | 10 ( 62%) |

[a] Subjects 116 and 117 were not included in the pharmacokinetic analyses because both received the sprinkle formulation, only (see Section IV.B.).
[b] All subjects characterized as "other" were of Hispanic descent.

**Table 3:** Summary of Discontinuation/Completion Information
(All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-359)

| | Treatment Sequence | | |
|---|---|---|---|
| | Market-Image/ Sprinkle (N=9) | Sprinkle/ Market-Image (N=9) | Total (N=18) |
| | n (%) | n (%) | n (%) |
| **Study Completed** | 9 (100) | 7 ( 78) | 16 ( 89) |
| **Study Discontinued** | | | |
| Adverse event | 0 | 1 ( 11) | 1 ( 6) |
| Other | 0 | 1 ( 11) | 1 ( 6) |
| **Total Discontinued** | 0 | 2 ( 22) | 2 ( 11) |

**Subject 116 (Protocol TOPMAT-PHI-359; dosage at discontinuation: topiramate 100 mg sprinkle formulation; primary reason for withdrawal: anemia, erythrocytes abnormal):** This 40-year-old, 63-kg woman was enrolled in Protocol TOPMAT-PHI-359 and randomized to the topiramate sprinkle formulation/market-image tablet treatment sequence. There were no clinically significant medical history abnormalities identified for this subject. The subject had low hemoglobin and markedly low hematocrit values (10.2 g/dL and 30.3%, respectively) on Day 1— before topiramate administration. The subject ingested the 100 mg topiramate sprinkle formulation on Day 1 and was discontinued on Day 4 because of anemia (investigator's verbatim term: low hemoglobin) and abnormal erythrocytes (investigator's verbatim term: low hematocrit), both of marked severity. Both of these adverse events were associated with abnormal hematologic clinical laboratory test values, as noted above. This subject had low hemoglobin (9.6 g/dL) and markedly low hematocrit (31.7%) values at the 60-hour post-treatment blood sample collection. Pre-treatment and 60-hour post-treatment red blood cell and platelet counts were within the normal range. The subject's white blood cell counts were within the normal range at her pre-treatment assessment and high (10.9 x $10^6$ cells/μL) at 60 hours post-treatment. The investigator considered the anemia and abnormal erythrocytes to be unlikely related to topiramate administration. Iron sulfate was prescribed to treat these adverse events. No follow-up laboratory test results were available.



**Table 7:** Incidence of Treatment-Emergent Adverse Events by Body System and Preferred Term
(All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-359)

| | Treatment Group | |
|---|---|---|
| **Body System** / Preferred term | Market-Image Tablet (N=16) n (%) | Sprinkle Formulation (N=18) n (%) |
| **Central And Peripheral Nervous System** | 8 ( 50) | 5 ( 28) |
| Paresthesia | 5 ( 31) | 4 ( 22) |
| Dizziness | 5 ( 31) | 3 ( 17) |
| Headache | 3 ( 19) | 3 ( 17) |
| Hypoesthesia | 4 ( 25) | 0 |
| **Gastrointestinal System** | 2 ( 13) | 3 ( 17) |
| Nausea | 1 ( 6) | 1 ( 6) |
| Vomiting | 2 ( 13) | 0 |
| Abdominal pain | 0 | 1 ( 6) |
| Diarrhea | 0 | 1 ( 6) |
| **Body As A Whole** | 2 ( 13) | 2 ( 11) |
| Pain | 1 ( 6) | 1 ( 6) |
| Asthenia | 1 ( 6) | 0 |
| Back pain | 1 ( 6) | 0 |
| Chest pain | 0 | 1 ( 6) |
| Influenza-like symptoms | 1 ( 6) | 0 |
| **Psychiatric** | 1 ( 6) | 1 ( 6) |
| Difficulty with concentration or attention | 0 | 1 ( 6) |
| Euphoria | 1 ( 6) | 0 |
| **Heart Rate And Rhythm** | 0 | 1 ( 6) |
| Palpitation | 0 | 1 ( 6) |
| **Red Blood Cells** | 0 | 1 ( 6) |
| Anemia | 0 | 1 ( 6) |
| Erythrocytes abnormal | 0 | 1 ( 6) |
| **Respiratory System** | 0 | 1 ( 6) |
| Coughing | 0 | 1 ( 6) |
| Sinusitis | 0 | 1 ( 6) |
| **Skin And Appendages** | 0 | 1 ( 6) |
| Pruritus | 0 | 1 ( 6) |
| Rash | 0 | 1 ( 6) |
| **Vascular (Extracardiac)** | 0 | 1 ( 6) |
| Flushing | 0 | 1 ( 6) |
| **Any Adverse Event** | 8 ( 50) | 7 ( 39) |

**Table 4:** Summary of Topiramate Pharmacokinetic Parameters (All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-359)

| | Market-Image Tablet (Treatment A; N=16) | | Sprinkle (Treatment B; N=16) | | % [a] |
|---|---|---|---|---|---|
| Parameter | Mean | (SD) | Mean | (SD) | Difference |
| $C_{max}$ (µg/mL) | 2.48 | (0.60) | 2.35 | (0.50) | -5.3% |
| $t_{max}$ (h) | 1.8 | (1.3) | 2.1 | (1.0) | 17.5% |
| $AUC_{0-*}$ (µg·h/mL)[b] | 60.2 | (13.7) | 57.9 | (15.0) | -3.8% |
| $AUC_{0-\infty}$ (µg·h/mL) | 70.6 | (15.9) | 69.2 | (18.8) | -1.9% |
| $k_e$ (1/h) | 0.0286 | (0.0071) | 0.0269 | (0.0054) | -5.9% |
| $t_{½}$ (h) | 25.5 | (5.5) | 26.7 | (5.4) | 4.7% |
| CL/F (mL/min) | 24.7 | (5.2) | 25.9 | (7.7) | 4.9% |

[a] With respect to Treatment A, (Treatment B - Treatment A) / Treatment A X 100.

[b] $AUC_{0-*}$ = AUC calculated to the last concentration above the quantification limit.

**Figure 1:** Mean Topiramate Plasma Concentration vs. Time Profiles from Sixteen Healthy Subjects Following a Single Oral 100 mg Dose of Topiramate (Protocol TOPMAT-PHI-359)



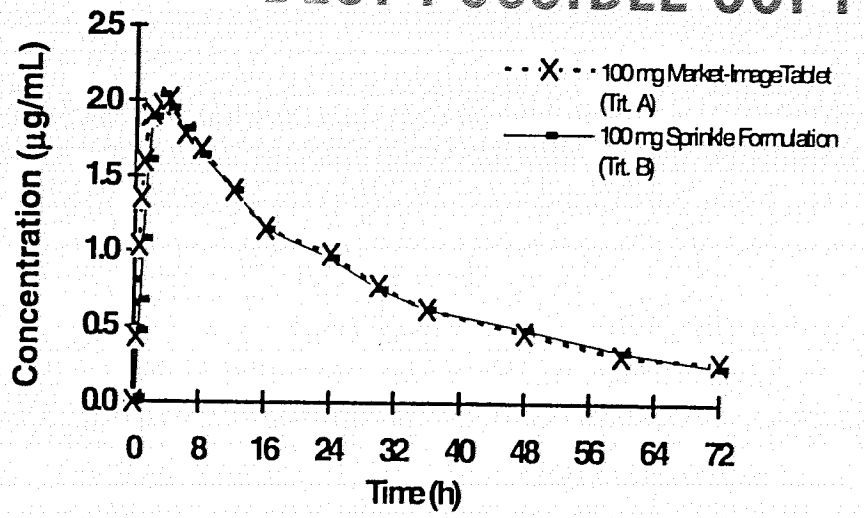


**Table 5.2:** 90% Confidence Intervals for ln-Transformed $C_{max}$, $AUC_{0-*}$ and $AUC_{0-\infty}$ After Normalizing Data for Treatment Formulation Potency (All Subjects Included in Pharmacokinetic Analysis; Protocol TOPMAT-PHI-359)

| | Estimated Ratio (%) of Geometric Means | 90% Confidence Interval for the Ratio of Means | |
|---|---|---|---|
| Parameter | (Sprinkle/Tablets) | Lower Bound [a] (% Reference) | Upper Bound [a] (% Reference) |
| $C_{max}$ | 95.92% | 87.65% | 104.96% |
| $AUC_{0-*}$ [b] | 94.74% | 90.08% | 99.64% |
| $AUC_{0-\infty}$ | 96.01% | 90.17% | 102.22% |

[a] Bounds as percent of the reference treatment (Treatment A/Tablets) geometric mean.

[b] $AUC_{0-*}$ = AUC calculated to the last concentration above the quantification limit.

**Table 5.1:** Summary of Statistical Comparisons of ln-Transformed Pharmacokinetic Parameters for Treatment Effects Without Normalizing Data for Treatment Formulation Potency (All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-359)

| | | | | 90% Confidence Interval for the Ratio of Means | |
|---|---|---|---|---|---|
| Parameter[a] | Results[b] of ANOVA | ANOVA[c] Power | Estimated Ratio (%) of Geometric Means (Sprinkle/Tablets) | Lower Bound [d] (% Reference) | Upper Bound [d] (% Reference) |
| $C_{max}$ | NS | 98% | 95.33% | 87.12% | 104.32% |
| $AUC_{0-*}$[e] | NS | >99% | 94.16% | 89.53% | 99.03% |
| $AUC_{0-\infty}$ | NS | >99% | 95.42% | 89.62% | 101.60% |
| Ranked $t_{max}$ | NS | ----[f] | ----[f] | ----[f] | ----[f] |
| Raw $t_{max}$ | NS | ----[f] | ----[f] | ----[f] | ----[f] |
| $k_e$ | NS | ----[f] | ----[f] | ----[f] | ----[f] |

[a] $C_{max}$, $AUC_{0-*}$, and $AUC_{0-\infty}$ were analyzed on ln-transformed scale.

[b] Analysis of variance model for a randomized two-way crossover design. NS = Not statistically significantly different (p>0.05).

[c] Power to detect a ratio of 125% (or 80%) in the means with a 5% level of significance.

[d] Bounds as percent of the reference treatment (Treatment A) geometric mean.

[e] $AUC_{0-*}$ = AUC calculated to the last concentration above the quantification limit

[f] ANOVA power, ratio of geometric means, and confidence intervals not calculated.

**Table 6:** Summary of Statistical Comparisons of Pharmacokinetic Parameters for Effects of Treatment Sequence Group, Period, and Treatment Effects, Without Normalizing for Treatment Formulation Potency (All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-359)

| | Root | Group Sequence Effect | | | Period Effect | | | Treatment Effect | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter[a] | MSE | F | df | p-value | F | df | p-value | F | df | p-value |
| $C_{max}$ | 0.144 | 0.0297 | 1,14 | 0.866 | 0.01 | 1,14 | 0.907 | 0.87 | 1,14 | 0.366 |
| $AUC_{0-*}$ | 0.080 | 0.0369 | 1,14 | 0.851 | 12.8 | 1,14 | 0.003 | 4.41 | 1,14 | 0.054 |
| $AUC_{0-\infty}$ | 0.100 | 0.0002 | 1,14 | 0.990 | 10.2 | 1,14 | 0.006 | 1.73 | 1,14 | 0.209 |
| Ranked $t_{max}$ | 7.183 | 0.0637 | 1.14 | 0.805 | 0.1431 | 1,14 | 0.711 | 1.62 | 1,14 | 0.224 |
| Raw $t_{max}$ | 0.907 | 0.072 | 1,14 | 0.784 | 0.0054 | 1,14 | 0.942 | 0.92 | 1,14 | 0.355 |
| ke | 0.005 | 0.7095 | 1,14 | 0.414 | 1.38 | 1,14 | 0.259 | 0.75 | 1,14 | 0.402 |

[a] Cmax, $AUC_{0-*}$, and $AUC_{0-\infty}$ were analyzed on ln-transformed scale.

**Table 2:** Demographic and Baseline Characteristics
(All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-360)

| | Subjects Included in PK Analyses (N=20) | All Subjects (N=24) |
|---|---|---|
| **Age (yrs)** | | |
| Mean (SD) | 33.1 (5.74) | 33.0 (5.38) |
| Median | 34.0 | 34.0 |
| Range | (20.0, 40.0) | (20.0, 40.0) |
| **Sex** | | |
| Male | 15 (75%) | 19 (79%) |
| Female | 5 (25%) | 5 (21%) |
| **Race** | | |
| White | 8 (40%) | 9 (38%) |
| Black | 3 (15%) | 3 (13%) |
| Asian | 0 | 0 |
| Other | 9 (45%) | 12 (50%) |
| **Height (cm)** | | |
| Mean (SD) | 170.3 (10.42) | 170.9 (10.07) |
| Median | 172.7 | 172.7 |
| Range | (152.4, 182.9) | (152.4,185.4) |
| **Weight (kg)** | | |
| Mean (SD) | 71.2 (9.91) | 72.2 (9.59) |
| Median | 70.8 | 71.7 |
| Range | (55.8, 87.7) | (55.8,87.7) |
| **Frame** | | |
| Small | 3 (15%) | 5 (21%) |
| Medium | 16 (80%) | 18 (75%) |
| Large | 1 (5%) | 1 (4%) |

**Table 3:** Summary of Discontinuation Information
(All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-360)

| Subject | Treatment Sequence[a] | Study Day Discontinued | Treatment Received | Reason for Discontinuation |
|---|---|---|---|---|
| 103 | C/B/A | 4 | C | lost to follow-up |
| 106 | A/B/C | 22[b] | A | protocol violation |
| 116 | B/C/A | 22[b,c] | B | protocol violation |
| 117 | B/A/C | 23[c] | B | subject choice |

[a] Treatment A = Sprinkle (fasted), Treatment B = Sprinkle (fed), Treatment C = Capsule (fasted).
[b] Subject 106 and 116 tested positive for alcohol and for drugs of abuse, respectively, and were discontinued before dosing in the second treatment period.
[c] Subjects 116 and 117 received an incorrect breakfast during period 0, and were restarted in the study. Both received study drug during period 0 and were discontinued before dosing in the second treatment period (period 1).

**Table 4:** Single Dose Plasma Topiramate Pharmacokinetic Parameters from Twenty Healthy Subjects Following a Single Oral 100 mg Dose of Topiramate
(All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)

| Parameters[a] | Applesauce Fasted | | Applesauce Fed | | % [b] Difference | Capsule Fasted | | % [b] Difference |
|---|---|---|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | 2.20 | (0.66) | 2.10 | (0.61) | -4.5% | 2.23 | (0.59) | 1.4% |
| $t_{max}$ (h) | 3.7 | (7.6) | 2.8 | (0.8) | -24.3% | 2.0 | (0.8) | -45.9% |
| AUC(0-*) (µg·h/mL) | 60.0 | (13.9) | 61.1 | (13.3) | 1.8%[c] | 61.1 | (11.8) | 1.8% |
| AUC(0-∞) (µg·h/mL) | 71.4 | (14.9) | 73.9 | (15.9) | 3.5% | 72.1 | (12.5) | 1.0% |
| $t_{½}$ (h) | 27.2 | (4.0) | 28.0 | (4.7) | 2.9% | 26.4 | (4.3) | -2.9% |
| $K_e$ (1/h) | 0.0261 | (0.0039) | 0.0254 | (0.0040) | -2.7% | 0.0269 | (0.0047) | 3.1% |
| CL/F (mL/min) | 24.3 | (4.9) | 23.6 | (5.3) | -2.9% | 23.7 | (3.9) | -2.5% |

[a] Data are the mean (SD), N=20.
[b] With respect to Applesauce Fasted Treatment.
[c] AUC calculated to the last concentration above the quantification limit.

**Figure 1:** Mean Topiramate Plasma Concentration vs. Time Profiles from Twenty Healthy Subjects Following a Single Oral 100 mg Dose of Topiramate
(All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)

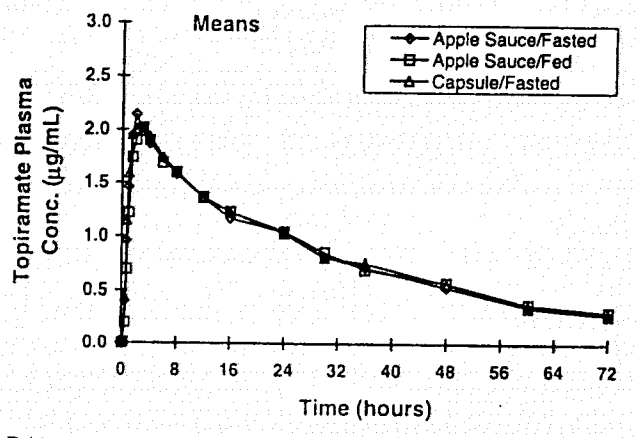


**Table 7:** Incidence of Treatment-Emergent Adverse Events by Body System and Preferred Term
(All Topiramate-Treated Subjects; Protocol TOPMAT-PHI-360)

| Body System / Preferred Term | TREATMENT: SPRINKLE (FASTED) N=21 | SPRINKLE (FED) N=20 | CAPSULE (FASTED) N=21 | SPRINKLE (FED)* N=8 | TOTAL N=24 |
|---|---|---|---|---|---|
| | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| **Central and Peripheral Nervous System** | | | | | |
| Dizziness | 1 (5) | 3 (15) | 3 (14) | 1 (13) | 6 (25) |
| Headache | 2 (10) | 1 (5) | 1 (5) | 0 | 3 (13) |
| Paresthesia | 0 | 0 | 1 (5) | 1 (13) | 2 (8) |
| Hypoesthesia | 1 (5) | 0 | 0 | 0 | 1 (4) |
| **Body As A Whole** | | | | | |
| Asthenia | 1 (5) | 0 | 1 (5) | 0 | 2 (8) |
| Back Pain | 0 | 1 (5) | 0 | 0 | 1 (4) |
| Pain | 1 (5) | 0 | 0 | 0 | 1 (4) |
| **Gastrointestinal System** | | | | | |
| Nausea | 0 | 0 | 1 (5) | 1 (13) | 1 (4) |
| Abdominal Pain | 0 | 1 (5) | 0 | 0 | 1 (4) |
| Flatulence | 0 | 0 | 0 | 1 (13) | 1 (4) |
| **Musculo-Skeletal System** | | | | | |
| Fracture Pathological | 1(5) | 1 (5) | 1 (5) | 0 | 1 (4) |
| **Psychiatric** | | | | | |
| Euphoria | 0 | 1 (5) | 1 (5) | 0 | 2 (8) |
| **Skin and Appendages** | | | | | |
| Pruritus | 0 | 0 | 1 (5) | 0 | 1 (4) |
| Rash | 0 | 0 | 1 (5) | 0 | 1 (4) |
| **Vascular (Extracardiac)** | | | | | |
| Flushing | 0 | 0 | 1 (5) | 0 | 1 (4) |
| Any Adverse Event | 4 (19) | 6 (30) | 6 (29) | 2 (25) | 9 (38) |

* Data are summarized for "FED" treatment period "0" in which these subjects received an incorrect breakfast, but received study drug.

**Table 5.1:** Summary of Statistical Comparison Results of Pharmacokinetic Parameters for Treatment Effects
(All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)

| Parameter | ANOVA Result[a] | ANOVA Power[b] |
|---|---|---|
| AUC (0-∞) | NS | >0.999 |
| AUC (0-*) | NS | >0.999 |
| $C_{max}$ | NS | >0.999 |
| Ranked $t_{max}$ | SIG | ---[c] |
| Raw $t_{max}$ | NS | ---[c] |
| $k_e$ | NS | ---[c] |

[a] Analysis of variance model for a randomized three-way crossover design. SIG = Statistically significantly different ($p \leq 0.05$). NS = Not statistically significantly different ($p > 0.05$).
[b] Power to detect a difference of ln(1.25) in the means on the log scale.
[c] ANOVA power and confidence intervals not calculated.

**Table 5.2:** Summary of Statistical Comparisons of Pharmacokinetic Parameters for Effects of Treatment Sequence Group, Period, and Treatment Effects
(All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)

| Parameter[a] | Root MSE | Group Sequence Effect F | df | p-value | Period Effect F | df | p-value | Treatment Effect F | df | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| AUC (0-∞) | 0.079 | 0.15 | 5,14 | 0.976 | 1.70 | 2,36 | 0.197 | 0.80 | 2,36 | 0.365 |
| AUC (0-*) | 0.071 | 0.12 | 5,14 | 0.986 | 1.87 | 2,36 | 0.169 | 1.04 | 2,36 | 0.458 |
| $C_{max}$ | 0.083 | 0.19 | 5,14 | 0.963 | 1.23 | 2,36 | 0.304 | 2.96 | 2,36 | 0.065 |
| Ranked $t_{max}$ | 13.58 | 0.54 | 5,14 | 0.746 | 1.73 | 2,36 | 0.191 | 7.34 | 2,36 | 0.002 |
| Raw $t_{max}$ | 4.376 | 0.82 | 5,14 | 0.557 | 0.78 | 2,36 | 0.468 | 0.76 | 2,36 | 0.477 |
| $k_e$ | 0.002 | 0.95 | 5,14 | 0.951 | 0.81 | 2,36 | 0.452 | 2.74 | 2,36 | 0.078 |

[a] $C_{max}$, AUC (0-∞), and AUC (0-*) were analyzed on ln-transformed scale

**Table 6.1:** 90% Confidence Intervals for the Ratio of the Mean ln-Transformed AUC (0-∞), AUC (0-*), and $C_{max}$ for the Applesauce/Fed to Applesauce/Fasted Treatment Comparisons
(All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)

| Parameter | Geometric Mean Applesauce Fasted | Geometric Mean Applesauce Fed | Estimated Ratio (%) of Geometric Means | 90% Confidence Interval for the Ratio of the Means Lower Bound[a] (% Reference) | Upper Bound[a] (% Reference) |
|---|---|---|---|---|---|
| AUC(0-∞) | 69.98 | 72.54 | 103.66 | 99.37 | 108.13 |
| AUC(0-*) | 58.50 | 59.86 | 102.32 | 98.51 | 106.29 |
| $C_{max}$ | 2.11 | 2.03 | 96.13 | 91.97 | 100.48 |

[a] Bounds as percent of the reference treatment (Applesauce/fasted) geometric mean.

**Table 6.2:** 90% Confidence Intervals for the Ratio of the Mean ln-Transformed AUC (0-∞), AUC (0-*), and $C_{max}$ for the Intact Capsules to Applesauce/Fasted Treatment Comparisons
(All Subjects Included in Pharmacokinetic Analyses; Protocol TOPMAT-PHI-360)

| Parameter | Geometric Mean Applesauce Fasted | Geometric Mean Capsule Fasted | Estimated Ratio (%) of Geometric Mean | 90% Confidence Interval for the Ratio of the Means Lower Bound[a] (% Reference) | Upper Bound[a] (% Reference) |
|---|---|---|---|---|---|
| AUC (0-∞) | 69.98 | 71.10 | 101.60 | 97.41 | 105.98 |
| AUC (0-*) | 58.50 | 60.03 | 102.62 | 98.79 | 106.59 |
| $C_{max}$ | 2.11 | 2.16 | 102.38 | 97.96 | 107.00 |

[a] Bounds as percent of the reference treatment (Applesauce/fasted) geometric mean



**Table 2:** Demographic and Baseline Characteristics

| Characteristics | Topiramate Sprinkle (N=15) |
|---|---|
| Sex | |
| Male | 10 |
| Female | 5 |
| Age (yrs) | |
| Mean (SD) | 8.1 (2.8) |
| Range | 3-13 |

**Table 3:** Subject Evaluation of Palatability of Topiramate Tablet and Sprinkle Formulations

| Rating | Score | Tablet (N=15) | Sprinkle (N=15) |
|---|---|---|---|
| Excellent | 1 | 2 | 0 |
| Very Good | 2 | 4 | 4 |
| Good | 3 | 2 | 4 |
| Average | 4 | 4 | 5 |
| Poor | 5 | 0 | 1 |
| Very Poor | 6 | 0 | 1 |
| Terrible | 7 | 3 | 0 |

**Table 4:** Distribution of Subjects by Evaluation of Palatability of the Sprinkle Formulation Compared with the Tablet Formulation

| TABLET ↓ / SPRINKLE → | Excellent | Very Good | Good | Average | Poor | Very Poor | Terrible |
|---|---|---|---|---|---|---|---|
| Excellent | | 1 | | 1 | | | |
| Very Good | | 1 | 2 | | 1 | | |
| Good | | 1 | 1 | | | | |
| Average | | | | 3[a] | | 1[b] | |
| Poor | | | | | | | |
| Very Poor | | | | | | | |
| Terrible | | 1 | 1 | 1 | | | |

[a] One of these subjects regularly spits out any tablet.

**Table 5:** Parental Assessment of Topiramate Sprinkle Formulation

| | Number (N=15) |
|---|---|
| Use of sprinkle rated as: | |
| Easy | 14 |
| Hard | 1 |
| Compared to tablet, sprinkle rated as: | |
| Worse | 7 |
| Better | 2 |
| Same | 5 |
| Not reported | 1 |