Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 11, 1996 DEC 16 1996

From: J. Todd Sahlroot, Ph.D.

Through: George Chi, Ph.D., Director, Division of Biometrics 1

Subject: NDA Amendment (Response to Approvable Letter) to NDA 20-505 for Topamax (topiramate)
Vol. 4 of Submission dated June 27, 1996

To: File (NDA 20-505)

Background

The Agency's December 29, 1995, Approvable letter to the sponsor granted a claim for adjunctive treatment in adults with partial onset seizures (PS). In the original NDA, the sponsor

Ostensibly to this end, they conducted statistical analyses which examined the

Phase compared with the Baseline Phase. In the Approvable Letter, the FDA stated that for a

This memo reviews the sponsor's analysis results.

Methods

Trials: Add-on trials: **YD** (PLB, 200, 400, 600mg), **YE** (PLB, 600, 800, 1000mg), **Y1** (PLB, 400mg), **Y2** (PLB, 600mg) **Y3** (PLB, 800mg) and **YF/YG** (PLB, 1000mg)

Patients: Randomized patients with ≥ 1 [1]

[1] This memo does not address the monotherapy indication also desired by the sponsor.

Double-Blind Phases.

Endpoint: Reduction in the proportion of PS evolvir
during the Double-Blind Phase compared with the Baseline Phase (Baseline proportion minus Double-Blind proportion). The proportion
was calculated as the number of PS with secondary generalization divided by the total number of PS.

Analysis: The sponsor compared the number of patients with a reduction in the proportion of PS evolving between topiramate and placebo treatment groups. Data were combined for the analyses in two ways. The first analysis compared topiramate to placebo by randomized dose (Sponsor's Table 1). Each comparison used data from trials that included that dosage. Comparisons were carried out using the Cochran-Mantel-Haenszel method stratified by trial. A second analysis compared topiramate to placebo for each trial. Topiramate dosages were combined within each trial for comparison with placebo (Sponsor's Table 2). This reviewer supplied two-sided p-values for Table 2 using Fisher's Exact Test.

Results

FDA Table 3 breaks out the data by trial and dosage. (Note: The data in Table 3 match the data in Appendix 3 in the submission but are slightly discrepant with Table 1 data. None of the disparities is crucial to the statistical inferences that follow.) Nominal significance was achieved for one dosage, 400mg (Table 1, p<.001) and for one trial, Y1 (Table 2, p=.004). Trial YD was close to nominal statistical significance (Table 2, p=.059) as was the 200mg vs placebo comparison (Table 1, p=.067). Trial YF/YG favored placebo (Table 2, p=.036). The positive result for 400mg is linked to the positive (or nearly positive) results for Y1 and YD, the only two trials utilizing this dosage. The positive results for Trials Y1 and YD were in turn partially driven by low placebo response rates (Table 3).

Across all trials and topiramate dosages, the response rate for topiramate was numerically greater than placebo, though only slightly. Fifty-five percent (55%, 99/181) of topiramate subjects (excluding 200mg) and 52% (46/88) of placebo subjects and experienced reductions in
ncluding the 200mg dosage, the topiramate response rate was 56% (110/198).

Conclusions

The result for 400mg was clearly statistically significant (p<.001). Additional considerations, however, call into question the validity of the result. Trials YD and Y1 had low placebo response rates, the lowest of the six add-on trials, which contributed to the statistical significance of the result. Furthermore, the result was not replicated at higher dosages, two of which had smaller response rates than placebo. An unusual aspect of the data (see Table 1) was that the smallest dosages (200, 400mg), including the only dosage (200mg) which did not demonstrate a clear effect on PS (p=.08), produced the smallest p-values in the conditional analyses of

seizures.

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

concur: Dr. Chi 12/16/96

cc: Arch NDA 20-505
HFD-120/Dr. Leber
HFD-120/Dr. Katz
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This memo consists of 3 pages of text and 3 tables.

AUG 22 1996

Topamax™ (topiramate)
25, 100, 200, mg tablets
NDA 20-505

R. W. Johnson Pharmaceutical Res Institute
Welsh & Mckean Road
Spring House, PA 19477-0776

Reviewer: Iftekhar Mahmood, Ph. D.
Submission Dates: March 29, 1996 and August 1, 1996.
Type of Submission: New Correspondence

OCTIIRN
AUG 26 1996

INTRODUCTION

Topamax™ (topiramate) is a chemical compound classified as a sulfamate-substituted monosaccharide, claimed by the Sponsor to be an antiepileptic. Chemically Topamax is designated as 2, 3:4,5-bis-O-(1-methylethylidene)-b-D-fructopyranose sulfamate. It may be available as 25, 100 and 200 mg round table

Topiramate is rapidly and well-absorbed after oral administration. Following 400 mg multiple oral dosing every 12 hours, peak plasma concentration of 27 µg/mL is reached in about two hours. There is no effect of food on the bioavailability of topiramate. The volume of distribution of topiramate following 100 to 1200 mg oral dose ranged from 0.55 l/kg to 0.8 l/kg. Plasma protein binding of topiramate is about 17 percent. Topiramate is not extensively metabolized and at least six minor inactive metabolites formed through hydroxylation, hydrolysis and glucuronidation have been identified from plasma and urine of humans. About 70% of the dose of topiramate is excreted unchanged in human urine. The mean elimination half-life of topiramate in humans is approximately 21 hrs. Oral clearance is approximately 29 ml/min in humans following oral administration. Clearance of topiramate was not affected by age, gender or race. The mean renal clearance of topiramate was 14 ml/min across 100-1200 mg single oral dose range and was 17 ml/min for 50 and 100 mg ql2h dosing regimens.

In this submission, the Sponsor has provided the following two pharmacokinetic studies:

Study #1. An open-label, single-center, safety, pharmacokinetic, and efficacy study of topiramate adjunctive therapy in pediatric subjects with epilepsy (Protocol TOPMAT-EPPD-001).

This study was conducted in 18 pediatric patients aged 4 to 17 years, who received topiramate (1, 3 and 9 mg/kg) in addition to other antiepileptic drugs. Mean topiramate clearance was 71 ml/min/70 kg in pediatric patients comedicated with enzyme-inducing anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital), whereas mean topiramate clearances in pediatric patients comedicated with non-enzyme-inducing anticonvulsants (e.g. valproic acid, gabapentin) was 33 ml/min/70 kg. On average, clearance values in the presence and in the absence of concomitant enzyme inducers were 54% (71 ml/min/70 kg in pediatric patients vs 46 ml/min/70 kg in adults) and 47% (33 ml/min/70 kg in children vs 22 ml/min/70 kg in adults) higher in pediatric patients, respectively, compared with those derived from historical adult controls (18-67 years). The steady-state topiramate plasma concentration was approximately 30% lower in pediatric patients than in adults. This study indicates that children eliminate topiramate at a faster rate than adults and dosage adjustment of topiramate may be required in pediatric patients.

The synopsis of this study can be found in Appendix 1.

Study #2. Comparative steady state bioavailability of norethindrone and ethinyl estradiol (Ortho-Novum) in female patients with epilepsy on valproic acid monotherapy before and after add-on TOPAMAX[R] Topiramate therapy (Protocol DM92355).

No significant differences in norethindrone pharmacokinetic parameters were observed in the presence of concomitant topiramate doses of 100, 200 and 400 mg q12h compared to baseline parameters in the absence of topiramate.

Concomitant topiramate therapy resulted in a decrease of ethinyl estradiol C_{max} and AUC by 25% to 30% and increased the oral clearance by 47% (range: 13-107%) at the highest topiramate dose of 400 mg given as q12 hour. These results suggest that the efficacy of oral contraceptives may be compromised by topiramate.

The synopsis of this study can be found in Appendix 2.

Comments to the Medical Reviewer:

1. Based upon the pediatric pharmacokinetic data and any available safety and efficacy information, appropriate sections of the labeling may need to be revised (e.g. indication, pediatric use, dosage and administration).

2. The oral contraceptive-topiramate interaction study demonstrates that the oral clearance of ethinyl estradiol is increased by 47% (range: 13-107%). Therefore, efficacy of oral contraceptives may be compromised by topiramate.

Comments to the Sponsor:

1. In the topiramate-oral contraceptive interaction study the effect of oral contraceptives on the pharmacokinetics of topiramate has not been evaluated. Ideally, drug-interaction study should be designed in such a way that the pharmacokinetic parameters can be estimated for both drugs in the presence and absence of each other under steady-state conditions.

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Recommendation:

The Sponsor is requested to incorporate all the labeling changes. Please forward Comment 1 and Labeling Comments to the Sponsor.

Iftekhar Mahmood, Ph.D. _____ 8/21/96

RD/FT initialed by Mohammad Hossain, Ph.D. _____ 8/22/96

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 20-505, HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), HFD-340 (Viswanathan), and HFD 870: Chron, Drug, Reviewer and FOI (HFD-19) files (Clarence Bott, PKLN, RM 13B-31).