

SYNOPSIS

<u>Name of Sponsor/Company:</u>	Ortho-McNeil Pharmaceutical, Inc.	
<u>Name of Finished Product:</u>	<u>TOPAMAX® (topiramate)</u>	
<u>Name of Active Ingredient(s):</u>	2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate	
Protocol No.: CR002662		
Title of Study: A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Migraine in Pediatric Subjects		
Coordinating Investigator: Multicenter Study		
Publication (Reference): None		
Study Period: 31 July 2001 to 02 September 2003		Phase of development: 3
Objectives: The objective of this study was to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine with or without aura in pediatric subjects.		
Methodology: This was a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel study, composed of 3 phases: pre-randomization (screening/washout and prospective baseline), double-blind and open-label extension. Only the data collected through the end of the double-blind phase are included in this report.		
<p>Eligibility was assessed during the pre-randomization phase, which lasted up to 56 days and included the screening/washout period and a 28-day prospective baseline period. All therapies being used for migraine prophylaxis were discontinued for a minimum of 2 weeks before the start of the prospective baseline period. Acute abortive medications were allowed for symptomatic relief of migraine and non-migraine headache episodes. Headache records were maintained by the subject's parent or guardian, with the subject's assistance (if appropriate), during this period. Eligibility was determined based on the number of 1) migraine episodes (as defined as the period from the onset of painful migraine symptoms to resolution of migraine pain or 24 hours after onset, whichever was shorter; migraine pain that recurred within 24 hours was considered to be the same episode; if painful symptoms persisted greater than 24 hours after their initial onset this was considered a new distinct episode), and 2) total headache-days (migraine and non-migraine) during the prospective baseline period.</p> <p>Subjects who completed the pre-randomization phase and who met the entrance criteria were randomized in a double-blind fashion, to 1 of 2 treatment groups in a 2:1 ratio (topiramate or placebo, respectively). The double-blind phase consisted of 2 periods: titration and maintenance. The titration period immediately followed the prospective baseline period and extended for approximately 56 days. All subjects received a starting dose of 15 mg/day of topiramate sprinkle capsules (or matching placebo) for the first week followed by an increase to 30 mg/day of topiramate sprinkle capsules (or matching placebo) for the second week. Starting at Week 3, subjects were to receive 50 mg/day of topiramate tablets (or matching placebo). Study medication was to be titrated to target dosages of 2.0-3.0 mg/kg/day of topiramate (or matching placebo) or until the subject's maximum tolerated dose (MTD) was achieved, whichever was lower. During the maintenance period, which lasted 84 days, the dose of study medication was to remain constant. Subjects were considered to have completed the double-blind phase of the study if they completed the maintenance period through Visit 8 (Day 141). Subjects who discontinued the study during any phase were encouraged to taper study medication at a rate of approximately 25-50 mg every 3 days until the subject was no longer taking study medication.</p>		
Number of Subjects (planned and analyzed): 150 subjects were planned for entry; 162 subjects were randomized. Efficacy analyses included 157 subjects in the Intent-to-Treat (ITT) Analysis Set (which included all subjects randomized to double-blind study medication who received at least 1 dose of study medication and for whom a post-baseline efficacy evaluation was available) and 126 subjects in the Evaluable-for-Efficacy Analysis Set (which included all subjects randomized who completed the study to Day 141 and had no major protocol violations). 157 subjects were analyzed for safety.		
Diagnosis and Main Criteria for Inclusion: Subjects with migraine with or without aura, as defined by the proposed International Headache Society (IHS) Classification of Pediatric Migraine. In addition, subjects were to be between 6 to 15 years of age, weigh more than 20 kg (44 lbs), have an average of 3-10 migraine-days per month during the 3 months (84 days) prior to screening, and experience no more than 15 headache-days per month. Select exclusion criteria included subjects who had previously failed topiramate therapy for migraine prophylaxis or those who had discontinued topiramate due to adverse events; had exclusively migraine aura without headache; had progressive neurological disorders or a structural disorder of the brain from birth, trauma or past infection; had overused analgesic		

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or migraine-specific agents for abortive therapy (e.g., triptans > 8 days per month and/or analgesics > 12 days per month); and had previously failed more than 2 adequate trials (defined as at least 1 month of treatment at a full therapeutic dose) of an established prophylactic anti-migraine regimen.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was administered orally as 15 mg sprinkle capsules (batch numbers R11439 or R11961) or 25 mg tablets (batch numbers R10967 or R11962).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was administered orally as 15 mg sprinkle capsules (batch number R11206 or R11963) or 25 mg tablets (batch numbers R10968 or R11964).

Duration of Treatment: The double-blind phase consisted of 2 periods: titration and maintenance. The titration period immediately followed the prospective baseline period and extended for approximately 56 days. Following the titration period, subjects entered the 84-day maintenance period.

Criteria for Evaluation:

Efficacy: The primary efficacy outcome was the number of migraine-days per month (ie, 28 days) during the double-blind treatment period relative to the prospective baseline period for each treatment group. Secondary efficacy outcomes included: monthly rate of migraine episodes, monthly rate of non-migraine headache episodes, monthly rate of total headache (migraine plus non-migraine) days, percentage of responders (subjects with a 50% or more, 75% or more and 100% reduction in mean monthly number of migraine-days), severity of migraines (Wong-Baker Faces Pain Rating Scale), duration of migraines, frequency and severity of associated migraine symptoms, frequency and dose of abortive medication, the Child Health Questionnaire (CHQ[®]PF50) and the Overall Global Evaluation.

Safety: Safety was assessed by the incidence, type and severity of reported adverse events, by the measurement of vital signs, physical examinations and clinical laboratory tests

Statistical Methods: For the primary efficacy analysis, the monthly rate of migraine days was assessed with a Cochran-Mantel-Haenszel (CMH) test with modridit scores and stratified by baseline rate of migraine days. This nonparametric test was chosen because the rate of migraine days was not normally distributed, therefore not meeting a necessary requirement of the analysis of covariance. The monthly rate of migraine episodes was also assessed with the CMH test. The other continuous headache variables (acute abortive medication rates, severity, duration, functional disability, frequency and severity of associated migraine symptoms, rate of non-migraine headaches and rate of total headaches) were assessed with an analysis of covariance with treatment and center as independent factors and respective baseline variable as a covariate. Analyses were performed for the ITT population and the Evaluable-for-Efficacy population. The percent of responders were analyzed using a Logistic regression with treatment and center as qualitative independent factors.

The 14 transformed scales (excluding Change in Health) and the 2 summary scores from the Child Health Questionnaire (CHQ PF50) were analyzed with an analysis of covariance with scores as the dependent measure, treatment and center as qualitative factors, and the corresponding baseline score as a covariate. The Change in Health was analyzed with a Cochran-Mantel-Haenszel Test with modridit scores stratified by baseline Change in Health score and center. Parental assessments of the overall effectiveness of the study medication were analyzed with a Cochran-Mantel-Haenszel Test with modridit scores and stratified by center.

SUMMARY - CONCLUSIONS

A total of 162 subjects were randomized in the study, of which 131 completed. The percentage of subjects who completed the study to Day 141 was 79.5% for the topiramate group (89/112) and 84% for the placebo group (42/50). The majority of the subjects in the ITT population were white (77.1%) and male (51.6%). The ages ranged from 6 to 16 years of age, with a mean age of 11.1 years.

EFFICACY RESULTS:

Subjects receiving topiramate experienced a lower mean monthly rate of migraine days in both the ITT and the Evaluable-for-Efficacy population. The mean monthly rate of migraine-days in the ITT population decreased 2.6 days in the topiramate group and 2.0 days in the placebo group; these between-group differences approached statistical significance (p=0.061). The mean monthly rate of migraine-days in the Evaluable-for-Efficacy population decreased significantly by 2.8 days in the topiramate group and 2.2 days in the placebo group (p=0.033).

During the maintenance period, the mean monthly rate of migraine-days in the ITT population decreased 3.1 days in the topiramate group and 2.3 days in the placebo group (p=0.026). The mean monthly rate of migraine-days in the Evaluable-for-Efficacy population during the maintenance period decreased 3.2 days in the topiramate group and 2.5 days in the placebo group (p=0.036).

In the ITT population, the proportion of responders with a 75% or more reduction in mean monthly rate of migraine

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episodes was greater in the topiramate group (32.4%) compared with the placebo group (14.3%, $p=0.021$), and in the Evaluable-for-Efficacy population, the topiramate group (35.3%) as compared with the placebo group (12.2%, $p=0.013$). Although the proportion of 50% responders in both the ITT population and the Evaluable-for-Efficacy population was greater in the topiramate group (54.6% and 60.0%, respectively) compared to the placebo group (46.9% and 46.3%, respectively), these proportions were not statistically significant ($p=0.396$ and $p=0.159$, respectively).

During the maintenance period, the reduction in the mean monthly rate of migraine episodes in the ITT population was greater for subjects in the topiramate group (2.8 episodes) than for subjects in the placebo group (2.1 episodes, $p=0.025$). In the Evaluable-for-Efficacy population, the reduction in the mean monthly rate of migraine episodes was numerically greater for subjects in the topiramate group (2.9 episodes) than for subjects in the placebo group (2.3 episodes, $p=0.038$).

Changes in the frequency of migraine-associated symptoms in the ITT population were similar between the 2 treatment groups, except for vomiting, where the mean change was -0.3 in the topiramate group as compared with -0.1 in the placebo group ($p=0.049$). In the Evaluable-for-Efficacy population, the changes were also similar between the 2 treatment groups except for vomiting, where the mean change in the topiramate group was -0.4 as compared with -0.2 in the placebo group ($p=0.009$). During the maintenance period, the mean changes were similar between the 2 treatment groups in the ITT population except for nausea, where the mean change in the topiramate group was -1.4 as compared with -0.7 in the placebo group ($p=0.048$). In the Evaluable-for-Efficacy population in the maintenance period, the mean changes were similar between the 2 treatment groups except for vomiting, where the mean change in the topiramate group was -0.4 as compared with -0.1 in the placebo group ($p=0.003$).

There were no statistically significant between-group differences for the other secondary efficacy parameters related to the headache record.

SAFETY RESULTS:

The most commonly reported adverse events in the topiramate group were upper respiratory tract infection (19.4%), anorexia (13.0%), pharyngitis (11.1%), sinusitis (10.2%), weight decrease (10.2%), and abdominal pain (10.2%). The most commonly reported adverse events in the placebo group were pharyngitis (20.4%), upper respiratory tract infection (16.3%), abdominal pain (12.2%), injury (12.2%), sinusitis, (12.2%) and fatigue (12.2%). Seven subjects (6.5%) in the topiramate group and 2 subjects (4.1%) in the placebo group experienced at least 1 adverse event which caused withdrawal from treatment. No clinically relevant differences between the 2 treatment groups in mean vital signs and clinical laboratory test results were observed. No deaths or life-threatening adverse events were reported during the study or within 30 days of study completion.

CONCLUSION:

Topiramate demonstrated a greater reduction in the monthly (28-day) migraine days in both the ITT and the Evaluable-for-Efficacy population. The numerical improvement in the rate of migraine days for the topiramate group in the ITT population (primary efficacy variable) did not reach statistical significance. The change in the rate of migraine days in the Evaluable-for-Efficacy population was statistically significant.

Analysis of specific secondary efficacy parameters demonstrated statistically significant differences between topiramate and placebo for migraine prophylaxis in this study during the maintenance period in the Evaluable-for-Efficacy population.

Treatment with topiramate in pediatric subjects for migraine prophylaxis was well tolerated with no unusual or unexpected adverse events reported.

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Date of the report: 12 August 2004

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