STUDY SYNOPSIS
Prepared by Linda Lynch, PhD

**Sponsor/Company**
Genzyme Corporation, Inc

**Trade Name**
Topamax

**Inactive Ingredients**
Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (100 and 200 mg tablets) and polysorbate 80.

**Title of Study**
Safety and Effectivness of Topiramate for Migraine Prevention in Adults With Chronic Headaches

**Investigators**
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**Study Centers**
14 United States locations

**Publication**
JAMA, February 25, 2004 – Vol 291, No. 965 - 973

**Studied Period**
2 years

**Date of First and Last Completed Enrollment**
Unknown

**Objective**
To assess the efficacy and safety of topiramate for migraine prevention in a large controlled study.

**Methodology**
Design: pilot placebo controlled study.

Inclusion Exclusion Criteria
Male and female subjects were required to have an established history of migraine, as assessed by the International Headache Society criteria, for at least 6 months prior to screening. Females had to be post menopausal, unable to bear children, or on a prescribed birth control medication. Frequency of migraine information was collected during a “baseline” phase.

Exclusion criteria: the use of long term medications including Beta blockers, tricyclic antidepressants, antiepileptic, calcium channel blockers, monoamine oxidase inhibitors, non-steroidal anti-inflammatory used daily, magnesium supplements at dose exceeding 600 mg/day, corticosteroids, history of nephrolithiasis, participating in other studies within 30 days, or had not taken topiramate for more than 2 weeks ever. Subjects were also excluded if they failed to respond to more than 2 adequate previous regimens of migraine preventive medications, if their onset of migraine occurred after age 50, or a history of nephrolithiasis.

Eligible patients entered a washout period for up to14 days, during which any migraine preventative medications were tapered. This period was followed by a prospective baseline phase of 28 days, during which headache and medication record information completed by patients was reviewed, and patients were permitted to take rescue medications. Subjects who successfully completed the baseline phase were assigned to one of 4 treatment groups according to a computer generated randomization schedule. Randomization was balanced by using permutated blocks of 4 and stratified by center.

Subjects randomized to the topiramate group received:
Topiramate 25 mg/day increasing 25 mg / week for 8 weeks or until maximum dose was reached, followed by 18 weeks of the highest dose daily in two equally divided doses morning and evening. The frequency and severity and symptoms of all headaches or auras were recorded by each patient in a diary, which was then transcribed into the patient's case record form at each clinical visit: 1, 29, 57, 85, 113, 141, and 183 days. Headaches were classified by using the subject's own judgment. Rescue meds were recorded for the type, amount, and duration of use. During specific intervals, hematologic, serum chemistry, and liver function tests were performed on all subjects, with physician exams occurring at the beginning and end of the study, and urinalysis being performed on the last visit only.

**Number of Patients**
The goal was to register 120 subjects per each treatment group (placebo, topiramate at 50 mg. day; topiramate at 100 mg/day; topiramate at 200mg.day). In total 693 subjects were enrolled and 210 did not make the screening criteria.

**Diagnosis and Main Inclusion Criteria**
All subjects were between the ages of 22 – 65, experiencing between 3 and 13 migraines in one week, but less than 15 headaches in a 28 day period. Each migraine experience had to last greater than 30 minutes.

**Test Product, Dose and Administration, Batch Number**
Subjects randomized to the topiramate group received:
Topiramate 25 mg/day increasing 25 mg / week for 8 weeks or until maximum dose was reached, followed by18 weeks of the highest dose daily in two equally divided doses, morning and evening.

**Duration of Treatment**
183 days

**Reference Therapy**
Allowable rescue medication included aspirin, acetaminophen, NSAIDs, ergot derivatives, triptans and opiods.

**CRITERIA FOR EVALUATION**

**Efficacy**
The primary analysis demonstrated that topiramate was associated with greater reductions in mean monthly migraine frequency than placebo. Mean monthly migraine frequency decreased from 5.4 at baseline to 4.1 during the double blind phase for patients treated with topiramate at 50mg/day, from 5.8 at baseline to 3.5 for patients treated with topiramate at 100mg/day, and from 5.1 to 3.0 for patients treated with topiramate at 200mg/d compared with a decrease from 5.6 to 4.5 for patients treated with

placebo. The change from baseline was statistically significant for patients treated with topiramate at 100 mg/d (P=.008), or 200mg/d (P<.001), in comparison with placebo but was not statistically significant for patient treated with topiramate at 50mg/d (P=.48) in comparison to placebo.

**Safety**
Safety was assessed by reports of adverse events, physical and neurologic examination, and clinical laboratory results. Treatment emergent adverse events commonly associated with topiramate use occurred in 10% of subjects treated with topiramate at 100mg/day and included: parenthesia 59%, fatigue 17%, anorexia 16%, weight loss 13%, hypoesthesia 13%, difficulty with memory 12% and nausea 12%.

## CONCLUSIONS

**Summary**
The results of this study demonstrate that topiramate is effective in migraine prevention, with results at least comparable to that of similar agents. This product was safe and had an acceptable level of tolerability, although an extended study is recommended.

**Efficacy Results**
Statistically significant efficacy in migraine prevention.

**Safety Results**
Topiramate appeared to be safe and had an accepted tolerability. Some of the most significant adverse events, involved weight loss that was dose dependant. Slow titration and initial target does of 100 mg/day in two divided doses was recommended.

**Final Conclusion**
The results demonstrate that topiramate is effective in migraine prevention, with results at least comparable to those of other similar agents.

**Date of Report**
3/28/05