DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Seth H.Z. Fischer
President
Ortho-McNeil Pharmaceutical, Inc
1000 Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Re: NDA # 20-505, 20-844
Topamax® (topiramate) Tablets
Topamax® (topiramate capsules) Sprinkles
MACMIS # 12547

WARNING LETTER

Dear Mr. Fischer:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a sales aid (2T10971), two case study flashcards (02T113 and 02T114), and a website (www.topamax.com) for Topamax® (topiramate) submitted by Ortho-McNeil Pharmaceutical, Inc. (Ortho-McNeil) under cover of Form FDA 2253. These promotional materials omit risk information about Topamax, in violation of the Federal Food, Drug, and Cosmetic Act (Act). 21 U.S.C. §§ 352(a), (n), 321(n). These materials raise serious public health concerns because they encourage the unsafe use of Topamax, including, particularly, in pediatric patients.

Background

The Indications and Usage section of the approved product labeling (PI) for Topamax states:

> **Epilepsy**
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> TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2 – 16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.
>
> **Migraine**
>
> TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headaches has not been studied.

TOPAMAX is associated with numerous risks. According to the Warnings and Precautions/Information for Patients sections of the PI:

> **Oligohidrosis and Hyperthermia**
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> Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.
>
> The majority of the reports have been in children. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.
>
> Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

According to the Warnings section:

> **Metabolic Acidosis**
>
> Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.
>
> In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence

of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut Syndrome or refractory partial onset seizures was 67% for TOPAMAX (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for TOPAMAX and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44 % for 200 mg/day, 39 % for 100 mg/day, 23 % for 50 mg/day, and 7 % for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value < 17 mEq/L and > 5 mEq/L decrease from pretreatment) in these trials was 11 % for 200 mg/day, 9 % for 100 mg/day, 2 % for 50 mg/day, and < 1 % for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

Omission of Material Fact

The promotional materials promote the use of Topamax in adults and children, and make safety and tolerability claims. For example, page one of the Sales Aid and a section of the website entitled "Physician Information," present the following claims:

- "The established worldwide safety record of Topirimate"
- "Well Tolerated"

The materials include some risk information, but fail to present any information about the risks of oligohidrosis, hyperthermia, and metabolic acidosis. For example, a section of the website entitled "Fact Sheet," includes only the following risk information:

- "When TOPAMAX® (5 to 9 mg/kg/day) was taken in clinical trials in combination with traditional AEDs, the most common side effects in children were excessive drowsiness, loss of appetite, fatigue, nervousness, difficulty with concentration/attention, weight loss, aggressive reaction to stimuli and memory difficulties. However, when they occurred, these effects were typically transient."
- "When TOPAMAX® (200 to 400 mg/day) was taken in clinical trials in combination with traditional AEDs, the most common side effects were sleepiness, dizziness, poor coordination, speech difficulties, slowed thinking (psychomotor slowing), blurred or double vision, memory difficulties and changes in sensation. However, when they occurred, these effects were generally temporary."

Additionally, the two Case Study Flashcards make the claim:

- In combination with other traditional antiepileptic drugs (AEDs), the most common side effects of TOPMAX in adults (200 to 400 mg/day) were somnolence, dizziness, ataxia, speech disorders and related problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, and diplopia; and in children (5 to 9 mg/kg/day), somnolence, anorexia, fatigue, nervousness, difficulty with concentration/attention, weight decrease, aggressive reaction, and memory difficulty.

Oligohidrosis and hyperthermia are very serious risks whose negative impact may be mitigated with appropriate monitoring. It is also noteworthy that the majority of reports of these adverse reactions have been in children. Metabolic acidosis is a very serious risk whose manifestations may include hyperventilation, cardiac arrhythmias or stupor. Monitoring in this case, measurement of serum bicarbonate, is quite important. Therefore, we view these adverse reactions of Topamax to be material when promoting the drug. Because the materials omit material risk information, they are false or misleading.

Conclusion and Requested Action

The sales aid, two case study flashcards, and website omit important risk information for Topamax® in violation of the Act. 21 U.S.C. §§ 352(a), (n) & 321(n).

DDMAC requests that Ortho-McNeil immediately cease the dissemination of promotional materials for Topamax® the same as or similar to those described above. Please submit a written response to this letter on or before September 29, 2004 describing your intent to comply with this request, listing all promotional materials for Topamax® the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious,

we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12547 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Topamax® comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violation discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications

Cc: William C. Weldon
CEO
Johnson & Johnson Pharmaceutical
Research & Development, L.L.C.

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/s/

Thomas Abrams
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