

# Refrigerated FluMist FDA-Approved for Ages 5-49

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A new formulation of intranasal influenza live virus vaccine that can be stored in a standard refrigerator, rather than kept frozen, has been approved by the Food and Drug Administration.

The new formulation of the trivalent vaccine, FluMist, is approved for healthy children and adults aged 5-49 years, and it will be available for the 2007-2008 flu sea-

son, according to a statement from the vaccine's manufacturer, MedImmune Inc. The company is seeking FDA approval of the refrigerated vaccine for use in children aged 12-59 months (1-5 years).

"This is a useful advance because the vaccine can be stored more easily and implemented better," Dr. Sarah Long, chief of the infectious diseases section at St. Christopher's Hospital for Children, Philadelphia, said in an interview.

But the new formulation's effect on physi-

cian practices will not necessarily be substantial at this time, added Dr. Long, who is also a member of the American Academy of Pediatrics' Red Book Committee.

"It will be very useful if it is approved for [younger] children," she noted.

The refrigerated formulation of FluMist will likely be appealing because of its ease of use, but the major factors driving influenza vaccination rates in primary care offices will continue to be cost (including reimbursement), vaccine supply and dis-

tribution, efficacy, and safety concerns, Dr. Jonathan Temte, of the University of Wisconsin, Madison, said in an interview.

"FluMist appears to have had better supply and distribution characteristics than the other influenza vaccines of late, but it is hampered by a higher price," said Dr. Temte, who also serves as American Academy of Family Physicians' liaison to the Center for Disease Control and Prevention's Advisory Committee on Immunization Practices.

That said, data have shown good efficacy for FluMist even in years when the vaccine was not well matched to the flu virus, he added.

Compared with injectable vaccine, FluMist provides better, longer lasting immunity and better cross-protection from year to year as the flu virus drifts, said Dr. Michael Pichichero, a private practice pediatrician and professor of microbiology and immunology at the University of Rochester (N.Y.). But the biggest drawback is cost. "Refrigeration is a minor advance in my opinion. If it were the same cost, it would be a no-brainer," he said.

Should universal influenza vaccination be recommended, the new FluMist formulation would be particularly appealing to goal more feasible. Most people are not willing to line up for an injection each year. At the same time, the refrigerated formulation broadens the potential for flu immunizations to be offered in locations outside of the physician's office, such as schools or clinics. But the caveat is that FluMist of either formulation can be given only to persons who are otherwise healthy, Dr. Long said.

The high cost will continue to be a major impediment to FluMist's utilization, although the new formulation would help to ensure a steadier vaccine supply if universal vaccination is advised, Dr. Temte added.

The original FluMist, which is also manufactured by MedImmune, has been available in a frozen formulation since its FDA approval in 2003.

**TOPAMAX®**  
(topiramate)  
Tablets

**TOPAMAX®**  
(topiramate capsules)  
Sprinkle Capsules

**Brief Summary of Full Prescribing Information for Migraine. CLINICAL STUDIES FOR OTHER INDICATIONS WILL HAVE DIFFERING ADVERSE EVENTS AND SAFETY CONCERNS. PLEASE SEE FULL PI FOR THIS INFORMATION REGARDING TOPAMAX® FOR EPILEPSY.**

**INDICATIONS AND USAGE**

**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 headache has not been studied.

**CONTRAINDICATIONS:** TOPAMAX® is contraindicated in patients with a history of hypersensitivity to any component of this product.

**WARNINGS: 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. Metabolic acidosis has been observed at doses as low as 50 mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/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, and 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, alkaline treatment should be considered. **Acute Myopia and Secondary Angle Closure Glaucoma:** A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX®. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX®, may be helpful. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss. **Oligohydrosis and Hyperthermia:** Oligohydrosis (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. **Cognitive/Neuropsychiatric Adverse Events:** Adults: Adverse events most often associated with the use of TOPAMAX® were related to the central nervous system. In adults, the most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue. **Cognitive-Related Dysfunction:** The majority of cognitive-related adverse events were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these events. Many of these events contributed to withdrawal from treatment (see **ADVERSE REACTIONS**, Table 1). In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day, and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse events and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse event. The most common cognitive adverse events occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive events. **Psychiatric/Behavioral Disturbances:** Psychiatric/behavioral disturbances (depression or mood problems) were dose-related for both the epilepsy and migraine populations. In the double blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred at a rate of 3/1000 patient years (13 events/3999 patient years) on topiramate versus 0 (0 events/1490 patient years) on placebo. One completed suicide was reported in a bipolar disorder trial in a patient on topiramate. **Somnolence/Fatigue:** Fatigue and somnolence were dose-related and more common in the titration phase.

**PRECAUTIONS: Hyperammonemia and Encephalopathy Associated with Concomitant Valproic Acid Use:** Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. **Kidney Stones:** As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients. An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorophenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation. **Paresthesia:** Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®. Paresthesia was more frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials versus the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment discontinuation. **Adjustment of Dose in Renal Failure:** The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal function (see **DOSE AND ADMINISTRATION**). **Decreased Hepatic Function:** In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. **Information for Patients:** Patients taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision or periorbital pain. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see **PRECAUTIONS: Kidney Stones**, for support regarding hydration as a preventative measure). Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance. Additional food intake may be considered if the patient is losing weight while on this medication. **Laboratory Tests:** Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended (see **WARNINGS**). **Drug Interactions:** In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. **Other Drug Interactions: Digoxin:** In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established. **CNS Depressants:** Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants. **Oral Contraceptives:** In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX® given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (16%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding. **Hydrochlorothiazide (HCTZ):** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C<sub>max</sub> increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination. **Metformin:** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C<sub>max</sub> and mean AUC<sub>0-12h</sub> increased by 16% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t<sub>1/2α</sub>. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When TOPAMAX® is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state. **Pioglitazone:** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the AUC<sub>0-12h</sub> of pioglitazone with no alteration in C<sub>max</sub> was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in C<sub>max,ss</sub> and AUC<sub>0-12h</sub>, respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in C<sub>max,ss</sub> and AUC<sub>0-12h</sub> of the active keto-metabolite. The clinical significance of these findings is not known. When TOPAMAX® is added to pioglitazone therapy or pioglitazone is added to TOPAMAX® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state. **Lithium:** Multiple dosing of topiramate 100 mg every 12 hrs decreased the AUC and C<sub>max</sub> of Lithium (300 mg every 8 hrs) by 20% (N=12, 6 M, 6 F). **Haloperidol:** The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 M, 7 F). **Amiripiline:** There was a 12% increase in AUC and C<sub>max</sub> for amiripiline (25 mg per day) in 18 normal subjects (9 male; 9 female) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amiripiline concentration in the presence of topiramate and any adjustments in amiripiline dose should be made according to the patient's clinical response and not on the basis of plasma levels. **Sumatriptan:** Multiple dosing of topiramate

(100 mg every 12 hrs) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg). **Risperidone:** There was a 25% decrease in exposure to risperidone (2 mg single dose) in 12 healthy volunteers (6 M, 6 F) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topiramate should be closely monitored for clinical response. **Propranolol:** Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 M, 17 F) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27M, 12F) had no effect on the exposure to topiramate at a dose of 200 mg/day of topiramate. **Dihydroergolamine:** Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 M, 12 F) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergolamine. Similarly, a 1 mg subcutaneous dose of dihydroergolamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study. **Others:** Concomitant use of TOPAMAX®, a carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorophenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided. **Drug/Laboratory Tests Interactions:** There are no known interactions of topiramate with commonly used laboratory tests. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady-state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m<sup>2</sup> basis). Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*. No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m<sup>2</sup> basis). **Pregnancy: Pregnancy Category C.** Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m<sup>2</sup> basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain. In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m<sup>2</sup> basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m<sup>2</sup> basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater. In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryofetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m<sup>2</sup> basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m<sup>2</sup> basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above. When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 0.2, 20, and 100 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m<sup>2</sup> basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m<sup>2</sup> basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater. In a rat embryofetal development study with a postnatal component (0.2, 2.5, 30, or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m<sup>2</sup> basis) and persistent reductions in body weight gain at 30 mg/kg (11 times the RHD on a mg/m<sup>2</sup> basis) and higher. There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In post-marketing experience, cases of hypoplasia have been reported in male infants exposed *in utero* to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. **Labor and Delivery:** In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day. The effect of TOPAMAX® on labor and delivery in humans is unknown. **Nursing Mothers:** Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing. **Pediatric Use:** Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia/rickets and may 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 (see **WARNINGS**). Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache. **Geriatric Use:** In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate ≤ 70 mL/min/1.73 m<sup>2</sup>) due to reduced clearance of topiramate (see **CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION** in the full PI). **Race and Gender Effects:** Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

**ADVERSE REACTIONS:** The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets. **Migraine:** In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse events with topiramate were mild or moderate in severity. Most adverse events occurred more frequently during the titration period than during the maintenance period. Table 1 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in any topiramate treatment group was at least 2% and was greater than that for placebo patients. **Table 1:** Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥ 2% in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients' **Body System/Adverse Event** followed by Placebo (N=445) first, TOPAMAX® Dosage (mg/day) 50 (N=235) second, 100 (N=386) third, 200 (N=514) fourth. **Body as a Whole - General Disorders:** Fatigue 11, 14, 15, 19; Injury 7, 9, 6, 6; Asthenia 1, <1, 2, 2; Fever 1, 1, 1, 2; Influenza-Like Symptoms <1, <1, <1, 2; Allergy <1, <1, <1, 2; **Central & Peripheral Nervous System Disorders:** Paresthesia 6, 35, 51, 49; Dizziness 10, 8, 9, 12; Hypoaesthesia 2, 6, 7, 8; Language Problems 2, 7, 6; Involuntary Muscle Contractions 1, 2, 2, 4; Ataxia <1, 1, 2, 2; Speech Disorders/Related Speech Problems <1, <1, <1, 2; **Gastro-Intestinal System Disorders:** Nausea 8, 9, 13, 14; Diarrhea 4, 9, 11, 11; Abdominal Pain 5, 6, 6, 7; Dyspepsia 3, 4, 4, 3; **Gastro-Intestinal System Disorders:** Dry Mouth 2, 2, 3, 5; Vomiting 2, 1, 2, 2, 3; **Gastroenteritis** 1, 3, 3, 2; **Hearing and Vestibular Disorders:** Tinnitus 1, <1, 1, 2; **Metabolic and Nutritional Disorders:** Weight Decrease 1, 6, 9, 11; Thirst <1, <1, <1, 2; **Musculoskeletal System Disorders:** Arthralgia 2, 7, 3, 1; **Neoplasms:** Neoplasm NOS <1, 2, <1, <1; **Psychiatric Disorders:** Anorexia 6, 9, 15, 14; Somnolence 5, 8, 7, 10; Difficulty with Memory NOS 2, 7, 7, 11; Difficulty with Concentration/Attention 2, 3, 6, 10; Insomnia 5, 6, 7, 6; Anxiety 3, 4, 5, 6; **Mood Disorders** 2, 3, 6, 5; **Depression** 4, 3, 4, 6; **Nervousness** 2, 4, 4, 4; **Confusion** 2, 2, 3, 4; **Psychomotor Alteration** 1, 3, 2, 4; **Libido Decreased** 1, 1, 1, 2; **Aggravated Depression** 1, 1, 2, 2; **Agitation** 1, 2, 2, 1; **Cognitive Mechanisms NOS** <1, <1, 2; **Reproductive Disorders, Female:** Menstrual Disorder 1, 2, 3, 2; **Reproductive Disorders, Male:** Ejaculation Premature 0, 3, 0, 0; **Resistance Mechanism Disorders:** Viral Infection 3, 4, 4, 3; **Otitis Media** <1, 2, <1, 1; **Respiratory System Disorders:** Upper Respiratory Tract Infection 12, 13, 14, 12; Sinusitis 6, 10, 6, 6; **Pharyngitis** 4, 5, 6, 2; **Coughing** 2, 2, 4, 3; **Bronchitis** 2, 3, 3, 3; **Dyspnea** 2, 1, 3, 2; **Rhinitis** 1, 1, 2, 2; **Skin and Appendages Disorders:** Pruritis 2, 4, 2, 2; **Special Sense Disorders:** Taste Perversion 1, 5, 8, 12; Taste Loss <1, 1, 1, 2; **Urinary System Disorders:** Urinary Tract Infection 2, 4, 2, 4; **Renal Calculus** 0, 0, 1, 2; **Vision Disorders:** Vision Abnormal <1, 1, 2, 3; **Blurred Vision** 2, 4, 2, 4; **Conjunctivitis** 1, 1, 2, 1; \*Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category. <sup>b</sup>Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for >50% of events coded as vision abnormal; a preferred term.

Of the 1,135 patients exposed to topiramate in the placebo-controlled studies, 23% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%). Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, -3%, and -4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively. Table 2 shows adverse events that were dose-dependent. Several central nervous system adverse events, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence.

**Table 2:** Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Migraine Trials: Adverse Event followed by Placebo (N=445) first, TOPAMAX® Dosage (mg/day) 50 (N=235) second, 100 (N=386) third, 200 (N=514) fourth. Paresthesia 6, 35, 51, 49; Fatigue 11, 14, 15, 19; Nausea 8, 9, 13, 14; Anorexia 6, 9, 15, 14; Dizziness 10, 8, 9, 12; Weight decrease 1, 6, 9, 11; Difficulty with Memory NOS 2, 7, 7, 11; Diarrhea 4, 9, 11, 11; Difficulty with Concentration/Attention 2, 3, 6, 10; Somnolence 5, 8, 7, 10; Hypoaesthesia 2, 6, 7, 8; Anxiety 3, 4, 5, 6; Depression 4, 3, 4, 6; Mood Problems 2, 3, 6, 5; Dry Mouth 2, 2, 3, 5; Confusion 2, 2, 3, 4; Involuntary Muscle Contractions 1, 2, 2, 4; Abnormal Vision <1, 1, 2, 3; Renal Calculus 0, 0, 1, 2. \*The incidence rate of the adverse event in the 200 mg/day group was ≥ 2% than the rate in both the placebo group and the 50 mg/day group.

**Other Adverse Events Observed During Migraine Clinical Trials:** Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1,367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The following additional adverse events that were not described earlier were reported by greater than 1% of the 1,367 topiramate-treated patients in the controlled clinical trials: **Body as a Whole:** Pain, chest pain, allergic reaction.

**Central & Peripheral Nervous System Disorders:** Headache, vertigo, tremor, sensory disturbance, migraine aggravated. **Gastrointestinal System Disorders:** Constipation, gastroesophageal reflux, tooth disorder. **Musculoskeletal System Disorders:** Myalgia, flatfoot, bleeding, and clotting disorders. **Epistaxis.** **Reproductive Disorders, Female:** Intermenstrual bleeding. **Resistance Mechanism Disorders:** Infection, genital moniliasis. **Respiratory System Disorders:** Pneumonia, asthma. **Skin and Appendages Disorders:** Rash, alopecia. **Vision Disorders:** Abnormal accommodation, eye pain. **Postmarketing and Other Experience:** In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving topiramate post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

**DRUG ABUSE AND DEPENDENCE:** The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

**OVERDOSE**  
Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®. Topiramate overdose has resulted in severe metabolic acidosis (see **WARNINGS**). A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days. In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.

