CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	Standard
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Division / Office	DNP / ODE 1
Reviewer Name(s)	Leonard P. Kapcala, M.D.
Review Completion Date	6/28/11
Established Name	Topiramate
(Proposed) Trade Name	Topamax
Therapeutic Class	Anticonvulsant / Anti-epileptic Drug
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Formulation(s)	Tablets and Sprinkle capsules
Dosing Regimen	Twice daily (BID) oral
Indication(s)	Partial Onset or Primary Generalized Tonic-Clonic Seizures
Intended Population(s)	Pediatric patients 2-9 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

- I am unable to make a regulatory recommendation, which would be based upon the assessment of risk vs benefit, because I have only conducted a review of various safety analyses for an assessment of safety. I have not made a determination of benefit of topiramate in pediatric patients 2 - < 10 years (i.e., 2-9 years old) for monotherapy because a controlled, clinical trial was not conducted for this indication and population and there were no clinical data to review for determining efficacy and benefit. An assessment and determination of benefit was made by Pharmacometric reviewers (Drs. Anshu Marathe and Yaning Wang) using a pharmacometric bridging approach based upon various pharmacokinetic and pharmacodynamic analyses of adults and pediatric patients (2-16 years) in adjunctive therapy and of adults and pediatric (10- 15 years, and 6-9 years) in monotherapy.

1.2 Safety Assessment

- Overall, I can conclude that topiramate is potentially "safe" for monotherapy of pediatric patients (2-9 years) based upon my unconventional safety review and making appropriate dosing recommendations.

- My safety review was unconventional/unorthodox because my safety assessment did not involve review of empirical safety/safety data from a specific clinical trial in which 2-9 year old patients had been studied in a randomized, double-blind, controlled study for determining the efficacy and safety of the initial monotherapy for partial onset or primary generalized, tonic-clonic seizures. When initial monotherapy of epilepsy was initially approved, the approval was for treating patients 10 years and older with topiramate despite the fact that the controlled, pivotal monotherapy trials had contained younger pediatric patients 6-9 years. At the time of initial monotherapy approval, there was concern that the safety experience was inadequate to support the safe use of monotherapy in patients 6-9 years. Consequently, the sponsor (in agreement with the DNP) planned to demonstrate the safety of topiramate as immunotherapy in patients 2-9 years based upon various pediatric safety data and corresponding analyses from other clinical trials for epilepsy and non-epilepsy indications. The expectation was that a major contribution of safety experience would be derived from adjunctive treatment of epilepsy in patients 2-9 years. However, toward the end of the initial review cycle, the Agency pharamcometric reviewers determined that the pharmacokinetic (PK) exposures of pediatric patients in the adjunctive studies were inadequate to support the safety of monotherapy of epilepsy of patients 2-9 years who would receive a lower limit, topiramate target dose of approximately 7 – 14 mg/kg/day (with mg/kg/day dosing inversely related to weight, and age for practical considerations) and an upper limit, topiramate target dose of approximately 11-22 mg/kg/day. The topiramate target dose was usually ~ 6 mg/kg/day, and often topiramate levels were significantly decreased by concomitant enzyme-inducing anti-epileptic drugs (EIAEDs) that can increase topiramate clearance (e.g., EIAEDs can decrease topiramate levels by ~ 50 %). As a result of this important, but unexpected discovery (i.e., the inadequacy of the originally submitted safety analyses to support the safety of the treatment of the indication of interest), there was a major change in the strategy of the safety review such that additional, new analyses were needed to support safety (see section 5.2 Review Strategy for Assessing Safety).

  Ordinarily, a safety review/assessment depends especially upon the empirical safety experience in controlled studies in which the same indication and the same population for whom efficacy was

investigated is evaluated. In contrast, my review of the safety for this indication for this population was primarily based upon imputation and many indirect inferences from other clinical safety data. There were three major categories of imputation and inferences for determining the safety of topiramate monotherapy of epilepsy for patients 2-9 years. First, the bulk of the relevant safety data supporting the safety of the indication under review was derived from topiramate treatment of a very different aged population (i.e., infants and toddlers, 1-24 months old) than the population of interest (2-9 years). Second, the bulk of the relevant safety data supporting the safety of the indication under review was derived from open-label, uncontrolled, topiramate treatment instead of from of randomized, double-blind, controlled studies. Third, the bulk of the relevant safety data supporting the safety of the indication under review was derived from a different treatment indication (adjunctive treatment of epilepsy) instead of from the indication of interest (initial monotherapy of epilepsy).

- My conclusion of the safety of treating patients 2-9 years with topiramate as initial monotherapy relied on the perspective that "young" pediatric patients 2-9 years and infants/toddlers ($\leq$ 2 years) treated with "high" dosing topiramate in open-label setting did not seem to experience unique treatment-emergent adverse events (TEAEs) compared to those experienced by older pediatric patients or adults. In particular, there did not appear to be any unique, medically serious adverse events experienced by young patients relative to the safety profile in the topiramate label. Although some of these TEAEs appeared to occur more frequently in younger pediatric patients than in older patients, these TEAEs did not seem uniquely severe in younger pts compared to older pts. Neither did they clearly appear to occur in a tremendously greater frequency in young pediatric patients 2-9 years than in than older patients during open-label treatment. I also thought that if treatment with relatively high doses of topiramate were reasonably "safe" and tolerated in very young pediatric patients (i.e., infants and toddlers 1-24 months), who were presumably exposed to topiramate levels that were as high (and possibly even higher because of decreased topiramate clearance in patients 1-24 months compared to pediatric patients $\geq$ 2 years), that similar treatment of older pediatric patients 2-9 years would be reasonably "safe" and tolerated.

- I also conclude that the dosing of topiramate as monotherapy in patients 2-9 years is reasonably "safe" because it involves slow titration of topiramate to a lower limit target dose and gradual titration to a higher dose (not to exceed the upper limit target in the label) if there is inadequate seizure control.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- No applicable

1.4 Recommendations for Postmarket Requirements and Commitments

- Randomized, double-blind, comparator, controlled, long-term (1 year) study of monotherapy epilepsy in pediatric patients 2-15 years old primarily focusing on topiramate effects on bone disease (by BMD via DXA), growth retardation/delay, kidney stones (via ultrasound), decreased sweating (with pilocarpine-induced sweat testing) and cognition/behavior.

2 Introduction and Regulatory Background

2.1 Product Information

Topiramate (TOPAMAX®) tablets and sprinkle capsules have been approved by the Food and Drug Administration (FDA) as adjunctive therapy for adults and pediatric patients aged 2 to 16 years with partial-onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and seizures associated with Lennox-Gastaut syndrome. Since its global introduction (18 July 1995), topiramate has been approved for antiepileptic adjunctive therapy for adults in more than 100 countries and for children ages 2 to 16 years in more than 70 countries. In the United States (US), topiramate is also approved as monotherapy in adult and pediatric patients (≥10 years of age in the US) with newly diagnosed POS or PGTC seizures (as demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment), and as migraine prophylaxis in adults.

The registered formulations of topiramate in the U.S. are coated oral tablets (25-, 50-, 100-, and 200-mg strengths; NDA 20-505) and coated beads in a gelatin capsule that can be swallowed whole or sprinkled on food (sprinkle capsules, containing 15 or 25 mg of topiramate; NDA 20-844).

The FDA approval (June 2005) for the use of topiramate as initial monotherapy in patients ≥10 years of age with POS or PGTC seizures included a postmarketing commitment specified by the Pediatric Research Equity Act (PREA). This commitment required Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) to conduct a clinical study of topiramate as initial monotherapy in patients ages 2 to <10 years old with POS or PGTC seizures, and to submit the final study report by 30 June 2010. In the September 2006 meeting with FDA (Type C: General Guidance), the sponsor proposed using a pharmacometric bridging model to support a monotherapy indication in pediatric patients ages 2 to <10 years with partial and generalized seizures in lieu of a new clinical study. This approach would utilize available pharmacokinetic (PK), efficacy and safety data from the topiramate clinical development program in adult and pediatric patients. At this meeting, the FDA agreed that the sponsor's plan was acceptable and provided additional recommendations in support of the proposed approach.

This supplemental New Drug Application (sNDA/NDA) submission presents the results of the pharmacometric bridging analyses along with supportive efficacy and safety information to fulfill the PREA commitment and to obtain a new indication and dose recommendations for the use of topiramate as initial monotherapy in patients ages 2 to <10 years with POS or PGTC seizures. The sponsor discussed the content and format of this supplemental NDA (sNDA) at a Type C meeting with FDA in February 2008.

2.2 Currently Available Treatments for Proposed Indications

The only approved new AEDs for monotherapy are topiramate (for 10 years and older) and oxcarbazepine that is approved for patients 4 years and older as a result of a pharmacometric bridging analysis NDA.

2.3 Availability of Proposed Active Ingredient in the United States

TOPAMAX® has been available for many years in the U.S. for various indications (see section 2.1) Generic topiramate is also available.

2.4 Important Safety Issues With Consideration to Related Drugs

Topiramate shares many safety issues/toxicities with zonisamide, another antiepileptic drug (AED) that is only approved for adjunctive treatment of partial epilepsy in adults. The most striking toxicities shared by these drugs include various adverse reactions on cognitive function, metabolic acidosis, and oligohydrosis/hyperthermia. The AEDs share several pharmacological actions including inhibition of carbonic anhydrase activity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor held many meetings with the Agency/Division of Neurology Product (DNP) to plan this NDA (see section 2.1).

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No new Division of Scientific Integrity (DSI inspections were conducted required because this NDA did not involve any new clinical studies.

3.2 Compliance with Good Clinical Practices

This NDA did not involve any new clinical studies. It relied on studies previously conducted and reviewed in various NDAs for various indications.

3.3 Financial Disclosures

Financial disclosure information was not required because this NDA did not involve any new clinical studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

Not applicable

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The precise mechanism by which topiramate exerts its anti-seizure or potential antinociceptive effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed four properties that may contribute to topiramate's antiepileptic efficacy.

• First, action potentials elicited repetitively by a sustained depolarization of the neurons are blocked by topiramate in a time-dependent manner, suggestive of a state and voltage dependent sodium channel blocking action.

• Second, topiramate increases the frequency at which γ-aminobutyrate (GABA) activates GABAA receptors, and enhances the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter. This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate GABAA receptors.1

• Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; non-NMDA) subtype of excitatory amino acid (glutamate) receptor, but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.2 These effects of topiramate are concentration-dependent within the range of 1 mM to 200 mM. It has a negative modulatory effect on Calcium channels which includes high voltage neurons (at least N or L types).

• Fourth, topiramate also inhibits some isoenzymes of carbonic anhydrase (CA-II and CA-IV). This pharmacologic effect is generally weaker than that of acetazolamide, a known carbonic anhydrase inhibitor.

4.4.2 Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

The following are considered to be major pharmacodynamic effects in humans that are described in the Warning and Precautions section of the label/package insert.

- Acute Myopia and Secondary Angle Closure
- Oligohidrosis and Hyperthermia
- Metabolic Acidosis
- Suicidal Behavior and Ideation
- Cognitive/Neuropsychiatric Adverse Reactions
- Fetal Toxicity (risk for oral clefts –cleft lip and/or cleft palate from topiramate exposure during pregnancy, and possible effects on decreased fetal growth, decreased fetal oxygenation, and fetal death, and the fetus' ability to tolerate labor because of metabolic acidosis)
- Sudden Unexplained Death in Epilepsy (SUDEP)
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid
- Kidney Stones
- Hypothermia with Concomitant Valproic Acid (VPA) Use
- Paresthesia

4.4.3 Pharmacokinetics

The sprinkle formulation is bioequivalent to the immediate-release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady-state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 µg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 µg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation,

hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Special Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high-efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20 to 30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required.

Hepatic Impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood

Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65 to 85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate ≤70 mL/min/1.73 m^2) is evident. It may be useful to monitor renal function in the elderly patient

Clearance of topiramate in adults was not affected by gender or race.

Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients ages aged 2 to 15 years. Patients received either no or a combination of other antiepileptic drugs. A population pharmacokinetic model was developed on the basis of pharmacokinetic data from relevant topiramate clinical studies. This dataset contained data from 1217 subjects including 258 pediatric patients aged 2 to 15 years (with 95 pediatric patients < 10 years of age).

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Pediatric patients on adjunctive treatment exhibited a higher oral clearance (L/h) of topiramate compared to patients on monotherapy. Oral clearance increased with body weight. Clearance was independent of dose. The plasma drug concentration for the same mg/kg dose may be lower in pediatric patients compared to adults and also in younger pediatric patients compared to older pediatric patients .

Drug-Drug Interactions

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in the table below here. In this table, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX®. was given alone.

Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] = Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.
TPM = Topiramate

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and TOPAMAX® has been associated with hyperammonemia with and without encephalopathy and hypothermia.

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 reactions, TOPAMAX® 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 (18%, 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 and 800 mg/day, there was no significant dose-dependent change in EE exposure for doses of 50 to 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.

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.

Hydrochlorothiazide

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate Cmax 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

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated.

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hr) and topiramate in plasma when metformin was given alone and when metformin and topiramate (100 mg every 12 hr) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and AUC_{0-12h} increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is not known. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear.

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 AUCτ,ss of pioglitazone with no alteration in Cmax,ss was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in Cmax,ss and AUCτ,ss respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in Cmax,ss and AUCτ,ss 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.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 22% decrease in C_{max} and a 25% reduction in AUC24 for glyburide during topiramate administration. Systemic exposure (AUC) of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), was also reduced by 13% and 15%, and C_{max} was reduced by 18% and 25%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

Lithium

In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose topiramate.

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 males, 7 females).

Amitriptyline

There was a 12% increase in AUC and Cmax for amitriptyline (25 mg per day) in 18 normal subjects (9 males, 9 females) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline 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 males, 10 females) did not affect the pharmacokinetics of single-dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone

When administered concomitantly with topiramate at escalating doses of 100, 250, and 400 mg/day, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this interaction is not likely to be of clinical significance.

Propranolol

Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 males, 17 females) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 males, 12 females) had no effect on the exposure to topiramate, at a dose of 200 mg/day of topiramate.

Dihydroergotamine

Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

Diltiazem
Co-administration of diltiazem (240 mg Cardizem CD®) with topiramate (150 mg/day) resulted in a 10% decrease in C_{max} and a 25% decrease in diltiazem AUC, a 27% decrease in C_{max} and an 18% decrease in des-acetyl diltiazem AUC, and no effect on N-desmethyl diltiazem. Co-administration of topiramate with diltiazem resulted in a 16% increase in C_{max} and a 19% increase in AUC_{12} of topiramate.

Venlafaxine

Multiple dosing of topiramate (150 mg/day) in healthy volunteers did not affect the pharmacokinetics of venlafaxine or O-desmethyl venlafaxine. Multiple dosing of venlafaxine (150 mg Effexor XR®) did not affect the pharmacokinetics of topiramate.

Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if TOPAMAX® is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 shows studies contributing to the Safety Summary Assessment.

Table 1 Studies Contributing to Safety Summary Assessment

Indication Seizure Type	Double-Blind Studies	Open-Label Studies
Epilepsy Adjunctive Therapy[a] Partial Onset Seizures	EPAJ-119, Y1, Y2, Y3, YD, YE, YF, YG, **YI**, **YP**	COGF-001, **EPAJ-111**, **EPPD-001**, **EPPD-002**[a], IP, M215, M216, M218, MET-001, MS220, YEP, YET, YC, YH, **YI**, **YJ**, YKP, YKT, YLT, YLTE, **YOL**, **YOLE**, YZL, YZT, YZW, OL phases of YF, YG, and **YP**
Primary Generalized Tonic-Clonic	**YTC**, **YTCE**	OL phases of **YTC** and **YTCE**
Lennox-Gastaut Syndrome	**YL**	**YK**, **YKE**, OL phase of **YL**
Typical Absence Seizures		**ABS-001**
Epilepsy Monotherapy Newly/Recently Diagnosed Epilepsy[b]	**TOPMAT-EPMN-104, -105, -106**	OL phases of **TOPMAT-EPMN-104, -106**
Migraine Prophylaxis	**TOPMAT-MIGR-001, -002, -003**[c], **CAPSS-122**, **TOPMAT-MIG-3006**	OL phases of **TOPMAT-MIGR-001, -002**, **CAPSS-122**
Bipolar Disorder	**TOPMAT-PDMD-009**	OL phase of **TOPMAT-PDMD-009**

Note: Studies that enrolled subjects <16 years of age are shown in bold; those that included subjects 2-9 years old are underlined (subjects aged 2-5 were only enrolled in the epilepsy adjunctive therapy studies).
[a] Study EPPD-002 included 27 subjects <2 years old at enrollment; these subjects are excluded from analysis.
[b] Partial onset seizures in recently diagnosed epilepsy for TOPMAT-EPMN-104; any type of seizure in newly diagnosed epilepsy for TOPMAT-EPMN-105; partial onset or primary generalized tonic-clonic seizures in newly diagnosed or recurrent epilepsy for TOPMAT-EPMN-106.
[c] Double-blind extension of TOPMAT-MIGR-003 not included.
Source: Appendix 1.2, Table 1.

Safety Evaluations and Analysis Sets

Safety Evaluations

Safety evaluations included the following:

- recording of adverse events;
- collection of body weight and height;
- clinical laboratory tests (hematology, chemistry, and urinalysis);
- evaluation of vital signs, including pulse rate, blood pressure, and body temperature;
- physical and/or neurologic examinations; and
- 12-lead ECG.

The types and timing of safety assessments differed across studies, and some evaluations were not performed in all studies (see individual results sections for further detail):

 Height and body mass index (BMI) are analyzed only for pediatric subjects, and post-baseline data are not available for all pediatric subjects.
 Standing and supine blood pressures were collected in a small number of studies; most studies collected blood pressure in the sitting position.
 Temperature was not collected in most studies.
 Serum ammonia was not collected in most studies.
 ECGs were not performed in all studies and were analyzed only for double-blind studies.

Additional safety evaluations, such as visual field examinations, were administered in some studies; these evaluations are not discussed in this safety summary.

Safety Analysis Sets

Safety analyses are based on available data from all subjects aged 2 years or older at the time of enrollment who were included in each study's safety analysis set. Safety analyses were performed using both pooled and individual analysis sets, as follows:

For *all studies* listed above in Table 1 :

 Safety analysis sets were pooled by study design type (double-blind or open-label) within each of the 4 indications: epilepsy adjunctive therapy, epilepsy monotherapy, migraine prophylaxis, and bipolar disorder.

For *selected double-blind studies* from Table 1, safety analysis sets were analyzed individually:

 Epilepsy adjunctive therapy: studies YP, YTC/YTCE, YL, YD, and YE
 Epilepsy monotherapy: studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN 106
 Migraine prophylaxis: studies TOPMAT-MIGR-001/002, TOPMAT-MIGR-003, TOPMAT-MIGR-3006, and CAPSS-122

Studies YTC and YTCE, as well as TOPMAT-MIGR-001 and -002, are pooled due to identical study designs.

Study Descriptions and Safety Analyses

Analyses of safety and related data included in this safety summary are described in the sections below here.

Study Descriptions

A total of 62 studies are included in this safety summary (when counting separately the double-blind and open-label periods performed under the same protocol number). These studies are described below by indication.

Epilepsy Adjunctive Therapy Studies

Topiramate as adjunctive epilepsy therapy has been evaluated in 13 double-blind studies and 34 open-label studies (6 extension phases of double-blind studies and 28 open-label studies; Table 2). Four of the double-blind studies and 9 of the open-label studies included subjects aged 2 to 9 years at enrollment.

Studies of topiramate as adjunctive therapy are grouped below by seizure type (POS, PGTC, seizures associated with Lennox-Gastaut syndrome, and typical absence seizures) and by double-blind or open-label study. The long-term studies were of variable length because they continued until terminated by the Sponsor as each country approved the marketing of topiramate and it became commercially available.

Table 2 **Description of Adjunctive Therapy Studies Contributing Data to the Safety Summary Assessment**

Protocol Number	Study Design
Partial Onset Seizures	
Double-Blind	
YD, YE, Y1, Y2, Y3, YF, YG	Randomized, double-blind, placebo-controlled, parallel-group trials designed to evaluate the efficacy and safety of topiramate as adjunctive therapy to standard antiepileptic drugs (AEDs) in subjects aged 18 to 65 years with refractory partial onset seizures with or without secondarily generalized seizures. Protocols YD and YE evaluated the safety and efficacy of 3 oral (target) topiramate dosages (200, 400, and 600 mg/day; 600, 800, and 1,000 mg/day, respectively), while Protocols Y1, Y2, and Y3 were conducted using a target dosage of 400, 600, or 800 mg/day, respectively. Protocols YF and YG were designed to evaluate the safety and efficacy of topiramate as adjunctive therapy (1,000 mg/day) in adult subjects receiving carbamazepine (YF) or phenytoin (YG). Each trial consisted of 2 phases, a prospective baseline phase, and a double-blind treatment phase during which subjects received an initial titration of topiramate to their assigned dosage (or maximally tolerated dosage, if less) and then maintained on this dosage for a period of 8 or 12 weeks.
YP	Randomized, double-blind, placebo-controlled trial that evaluated topiramate (target) dosages of 125, 175, 225, and 400 mg/day based on subject weight to approximately 6 mg/kg/day as adjunctive therapy in pediatric subjects aged 2 to 16 years with uncontrolled partial onset seizures with or without secondarily generalized seizures. The trial consisted of a baseline phase (8 weeks) and a double-blind phase (approximately 16 weeks).
YI	Parallel-group design to evaluate the safety and efficacy of 2 dosages of topiramate (100 and 1,000 mg/day) administered in subjects ≥14 years of age with refractory partial onset seizures while their background AEDs were gradually withdrawn. The trial included a screening phase, a baseline phase (8 weeks), an open-label treatment phase (1 week), and a double-blind treatment phase (16 weeks).
EPAJ-119	Randomized, double-blind, parallel-group, placebo-controlled study designed to examine the efficacy of topiramate 200 mg/day as adjunctive therapy to carbamazepine (with or without another antiepileptic drug) in adult subjects aged 18 to 65 years with partial onset epilepsy. Two titration rates of topiramate (25 mg/day per week and 50 mg/day per week) were compared with regard to the tolerability and efficacy. The study consisted of a 4-week baseline phase, a 12-week double-blind phase, and a blinded transition to commercial use (or tapered withdrawal).
Open-Label	
YKP/YKT, YEP/YET, YF/YG	Adult subjects completing the treatment period in double-blind Protocols YD, YE, Y1, Y2, and Y3 were able to receive long-term, open-label adjunctive treatment with topiramate (≤1,600 mg/day) under Protocols YKP/YKT (for Protocols YD and YE) and YEP/YET (for Protocols Y1, Y2, and Y3) for up to 4 years. Subjects completing double-blind Protocols YF and YG could receive long-term adjunctive treatment under Protocol YF/YG extension.

Table 2 (Continued) **Description of Adjunctive Therapy Studies Contributing Data to the Safety Assessment**

Protocol Number	Study Design
Partial Onset Seizures (continued)	
Open-Label (continued)	
YP	Pediatric subjects 2 to 16 years of age completing the 16-week double-blind phase of Study YP were able to enter the open extension phase, which consisted of 2 periods, an initial 42-day double-blind period and an open-label treatment period. Subjects who received topiramate during the double-blind phase of Study YP continued to receive topiramate at the dosage they had been maintained on during the stabilization period. During the initial 42-day period of the extension, subjects who received placebo during the double-blind phase had topiramate substituted for placebo and titrated to a maximum daily dosage of 125, 175, 225, or 400 mg/day based on subject weight or to the maximum tolerated dose, whichever was less. After extension day 42, the topiramate dosage could be further increased (≤1,600 mg/day).
YI, YJ	Subjects completing the double-blind portion of Protocols YI and YJ (in subjects ≥14 years of age with partial onset seizures) were able to receive open-label topiramate monotherapy (≤1,000 mg/day) in the open-label extensions of these studies.
IP	Evaluated the safety of 100 mg/day topiramate administered for 7 days as adjunctive therapy in adult subjects with refractory partial onset seizures.
YH	Evaluated various topiramate dose titration schedules (maximum dosage ≤1,000 mg/day) in adults with refractory partial onset seizures over a 6-week period while their background AEDs were gradually reduced.
YOL, YOLE	Long-term, open-label safety studies in subjects ≥14 years of age with any seizure type in which topiramate (≤1,600 mg/day) was administered as either adjunctive therapy or as monotherapy.
MS-215, MS-216, MS-218, YZL, YZT, YZW	Open-label pharmacokinetic studies in adults with simple or complex partial epilepsy that evaluated potential interactions of topiramate (100 to 1,200 mg/day for 12 to 18 weeks) with standard AEDs.
MS-220	Evaluated the potential interaction between topiramate and the oral contraceptive combination of norethindrone and ethinyl estradiol in adults.
YC	Evaluated the safety and efficacy of topiramate (≤1,600 mg/day) administered as adjunctive therapy in adults with partial onset seizures. The initial study was 8 weeks, but was extended a total of 3 years.
COGF-001	Randomized, open-label study that used a battery of neuropsychometric tests to evaluate the cognitive effects of topiramate (target dosage of 400 mg/day) and valproic acid administered as an add-on therapy to baseline carbamazepine treatment in adult subjects with partial onset seizures. The trial included a 4-week retrospective baseline phase and a 20-week add-on phase.

Table 2 (Continued) **Description of Adjunctive Therapy Studies Contributing Data to the Safety Assessment**

Protocol Number	Study Design
Partial Onset Seizures (continued)	
Open-Label (continued)	
EPPD-001	Open-label trial evaluating the pharmacokinetics and safety of topiramate administered as adjunctive therapy in pediatric subjects between the ages of 4 and 17 years with any seizure type. Each subject received topiramate dosages of 1, 3, 6, and 9 mg/kg/day; each dosage was administered for 7 days. During the extension phase of the study, subjects <14 years of age could have their dosage increased to a maximum of 30 mg/kg/day (≤1,600 mg/day), while subjects ≥14 years of age could receive a maximum of 2,400 mg/day.
EPPD-002	Open-label trial to evaluate the efficacy and safety of topiramate adjunctive therapy in pediatric subjects aged 1 to 18 years with inadequately controlled epilepsy. Following a 4-week baseline phase, topiramate was titrated to a minimum effective dose or a maximum tolerated dose (≤24 mg/kg/day); once a subject's dosage was stabilized, concomitant AEDs may have been withdrawn to attempt topiramate monotherapy. After the 6-month core phase, subjects could continue open-label treatment in the extension phase.
MET-001	Open-label study designed to assess possible predictors of weight loss in adults with partial onset seizures treated with topiramate (target dosage 400 mg/day, with a maximum allowable dosage of 1,000 mg/day) as adjunctive treatment for up to 1 year.
EPAJ-111	Open-label study to investigate the long-term safety and efficacy of topiramate as adjuvant therapy (target dosage of 200 to 1,600 mg/day, with an option to attempt monotherapy) in subjects aged 12 years and older with partial onset seizures. The study included a 12-week retrospective baseline and a core phase consisting of a 4-month titration period and a 6-month maintenance period.
YLT, YLTE	Long-term extension of open-label adjunctive treatment with topiramate (≤1,600 mg/day) for adult subjects from Protocols YCO2, YKT, YKP, MS-215, MS-216, and MS-218 (YLT), and YEP and YET (YLTE).
Primary Generalized Tonic-Clonic	
Double-Blind	
YTC, YTCE	Randomized, double-blind, placebo-controlled trials in pediatric subjects ≥4 years of age and adult subjects with refractory primary generalized tonic-clonic seizures, with or without other seizure types. Subjects were randomly assigned in equal numbers to receive either topiramate at a target dosage of approximately 6 mg/kg/day, maximum ≤9.3 mg/kg/day, or placebo twice daily during the double-blind phase of the study, which included an 8-week titration period and a 12-week stabilization period.
Open-Label	
YTC, YTCE	Subjects who completed the double-blind phases of YTC and YTCE could enter the open-label extension phases following a blinded transition to open-label topiramate as monotherapy or adjunctive therapy (maximum of 175 mg/day for subjects weighing 25 to 33.9 kg, 225 mg/day for subjects weighing 34 to 42.9 kg, and 400 mg/day for subjects weighing 43 kg or more).

Table 2 (Continued) **Description of Adjunctive Therapy Studies Contributing Data to the Safety Assessment**

Protocol Number	Study Design
Lennox-Gastaut Syndrome	
Double-Blind	
YL	Multicenter, randomized, double-blind, placebo-controlled trial that evaluated topiramate at a target dosage of 6 mg/kg/day (≤600 mg/day) as adjunctive therapy in subjects 12 months of age or older with Lennox-Gastaut syndrome. The trial included a baseline phase (4 weeks), a double-blind treatment phase (11 weeks in duration), and an open-label extension phase.
Open-Label	
YK, YKE	Open-label studies that evaluated topiramate (≤9 mg/kg/day, not to exceed 800 mg/day) administered as adjunctive therapy in pediatric subjects ages 4 to 18 years with Lennox-Gastaut syndrome for 8 weeks.
YL	In the open-label extension of study YL, subjects received topiramate as either monotherapy or adjunctive therapy (subjects <12 years of age, up to 800 mg/day, and subjects ≥12 years of age, up to 1,600 mg/day, not to exceed 9 mg/kg/day).
Typical Absence Seizures	
Open-Label	
ABS-001	Open-label, single-center study of topiramate (target dose 12 mg/kg/day) as adjunctive therapy in pediatric subjects ages 4 to 11 years with typical absence seizures. The study included a 6-week open-label treatment (core) phase and an extension phase.

Epilepsy Monotherapy Studies

Topiramate as monotherapy for newly or recently diagnosed partial onset epilepsy has been evaluated in 3 double-blind Phase 3 studies, each of which included subjects between the ages of 6 and 9 at enrollment (Table 3). Two of the 3 studies (TOPMAT-EPMN-106 and TOPMAT-EPMN-104) also had open-label extensions that contributed safety data for this summary.

Table 3 Description of Monotherapy Studies Contributing to the Safety Summary Assessment

Protocol Number(s)	Study Design
Double-Blind	
TOPMAT-EPMN-106	Randomized, double-blind, parallel-group study comparing the safety and efficacy of 2 dosages of topiramate (50 or 400 mg/day) as monotherapy for the treatment of pediatric or adult subjects (body weight ≥25 kg), with newly diagnosed or recurrent epilepsy. There were 4 phases: baseline (3-month retrospective), open-label treatment (topiramate 25 mg/day for 7 days to ascertain tolerability), double-blind (50 mg/day or 400 mg/day, with a 42-day titration period followed by a stabilization period), and long-term extension.
TOPMAT-EPMN-104	Randomized, double-blind, parallel-group study comparing the safety and efficacy of a low dosage (25 or 50 mg/day based on body weight) and a high dosage (200 or 500 mg/day based on body weight) of topiramate as monotherapy for the treatment of recently diagnosed partial onset epilepsy in pediatric (≥3 years of age) and adult subjects. The study included 4 phases: a retrospective baseline phase (3 months), an open-label treatment phase (7 days), a double-blind treatment phase (variable duration), and a long-term extension.
TOPMAT-EPMN-105	Randomized, double-blind, parallel group trial that compared the efficacy and safety of 2 doses (100 and 200 mg/day) of topiramate monotherapy to standard monotherapy (either carbamazepine 600 mg/day or valproate 1,250 mg/day) in adult and pediatric (≥6 years of age) subjects with newly diagnosed epilepsy. The study included 3 phases: baseline (7 days), double-blind (5-week titration followed by stabilization of variable duration), and blinded crossover extension of variable duration in which subjects could receive the alternative study medication within their treatment branch under blinded conditions.
Open-Label	
TOPMAT-EPMN-104, TOPMAT-EPMN-106	Open-label extensions of topiramate monotherapy up to a maximum of 1,600 mg/day for subjects ≥14 years (for subjects <14 years of age, up to 24 mg/kg/day).

Studies in Non-Epilepsy Indications

Data from 5 double-blind Phase 3 studies of topiramate as prophylaxis for migraine are presented in this safety summary (Table 4). Three of these studies (TOPMAT-MIGR- 001, TOPMAT-MIGR-002, and CAPSS-122) also had open-label extensions that contributed safety data for this summary. Only 1 of these studies, CAPSS-122, included subjects between the ages of 6 and 9 years at enrollment.

One Phase 3 study of topiramate for the treatment of bipolar disorder contributed data to this safety summary (Table 4). This study had both a double-blind phase and an open-label phase and included subjects between the ages of 6 and 9 years inclusive at enrollment.

Table 4 **Description of Studies in Non-Epilepsy Indications Contributing Data to the Safety Summary Assessment**

Protocol Number(s)	Study Design
Migraine Prophylaxis Studies	
Double-Blind	
TOPMAT-MIGR-001, TOPMAT-MIGR-002	Randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of topiramate (50, 100, or 200 mg/day) versus placebo for migraine prophylaxis in subjects between 12 and 65 years of age. Each study had 5 phases: baseline (14-day washout and 28-day prospective baseline period), double-blind (8-week titration period and 18-week maintenance period), blinded transition, open-label extension, and 2-week taper/exit.
TOPMAT-MIGR-003	Randomized, double-blind, parallel-group trial that evaluated the efficacy and safety of 2 doses of topiramate (100 and 200 mg/day) versus placebo and propranolol 160 mg/day for migraine prophylaxis in subjects 12 to 65 years of age. The trial included 4 phases: baseline (14-day washout and 28-day prospective baseline period), core double-blind (8-week titration and 18-week maintenance), blinded extension, and taper/exit (up to 7 weeks). During the blinded extension phase, subjects were to continue to receive the same dose of study medication for up to 12 months after the last subject was randomized or until they were withdrawn.
CAPSS-122	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine with or without aura in pediatric subjects ages 6-15 years. The study had 3 phases: pre-randomization (screening/washout and 28-day prospective baseline), double-blind (8-week titration and 12-week maintenance), and open-label extension (12 weeks). Study medication was to be titrated to target dosages of 2.0 to 3.0 mg/kg/day of topiramate (or matching placebo) or until the subject's maximum tolerated dose was achieved.
TOPMAT-MIG-3006	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the tolerability, safety, and efficacy of topiramate 50 or 100 mg/day as prophylaxis in pediatric subjects ages 12 to 17 years with episodic migraine headaches with or without aura. The study had 3 phases: a ≤9-week pretreatment phase, a 16-week double-blind treatment phase (including a 4-week titration period and a 12-week maintenance period), and a posttreatment phase (including a 2-week taper of blinded medication, a 4-week study drug-free period, and a follow-up visit).
Open-Label	
TOPMAT-MIGR-001, TOPMAT-MIGR-002	Long-term extension of open-label topiramate (maximum 1,600 mg/day).
CAPSS-122	Twelve-week extension of open-label topiramate (target dose 2.0 to 3.0 mg/kg/day or maximum tolerated dose).

Table 4 (Continued) Description of Studies in Non-Epilepsy Indications Contributing Data to the Safety Summary Assessment

Protocol Number(s)	Study Design
Bipolar Disorder Study	
Double-Blind and Open-Label	
TOPMAT-PDMD-009[a]	Randomized, double-blind, placebo-controlled, parallel-group study of topiramate monotherapy (up to a maximum of 400 mg/day based on tolerability) versus placebo in adolescents 13 to 17 years old with manic or mixed episodes of Bipolar I Disorder by DSM IV criteria. The study consisted of 3 phases: a screening phase (variable duration), a 28-day double-blind treatment phase, and an optional open-label phase (100 to 600 mg/day) for 6 months or more.

[a] The sponsor terminated this study prematurely; thus, only 56 of the planned 230 subjects were enrolled and completed the 4-week double-blind phase of the study. A total of 4 of 43 subjects completed the open-label phase of the study. Note that the age range for enrollment in this study was originally 6-15 years; however, this was changed to 13-17 years after 8 subjects had been enrolled, thus there were a few subjects as young as 6 years of age.

Safety Analyses

All analyses were performed by treatment group, age subgroup, and overall. The ranges used for pediatric age subgroups were 2-5, 6-9, 2-9, 10-15, and 2-15 years, based on the age at enrollment (note that only the epilepsy adjunctive therapy studies include a 2-5 age group; for all other indications, the youngest age group is 6-9). Definitions for age subgroups, treatment groups (in pooled analyses), visit windows, and titration and maintenance periods are provided in Section 3.1 of the SAP.

Analyses performed for this safety summary are as follows (note that not all studies collected the required data for each analysis) :

- Demographics and baseline characteristics (age, race, sex, height, weight, and BMI)
- Extent of exposure to study medication (duration and dosage)
- Treatment-emergent adverse events (TEAEs), including
- common AEs
- serious adverse events (SAEs)
- AEs that lead to treatment discontinuation
- AEs reflecting cognitive-related dysfunction (for double-blind studies only)
- AEs by time of onset relative to dose titration and attainment of maintenance dose (for double-blind studies only)
- AEs by concomitant use of inducing/non-inducing antiepileptic drugs (AEDs; for the 2 to 9 age group in the double-blind adjunctive therapy studies only)
- Clinical laboratory test values (hematology, chemistry, and urinalysis), including summaries of values and change from baseline, shifts based on normal range values, and incidence of abnormal and markedly abnormal values.
- Vital signs measurements (temperature, sitting blood pressure and pulse, standing and supine blood pressure measurements), including summaries of values and change from baseline, and incidence of abnormal values.
- ECG parameters (heart rate, PR interval, QRS interval, QT interval, QTcB [Bazett correction], QTcF [Fridericia correction], and QTcLD [linear-derived correction]), including the incidence of QTc values $\geq$ 500 ms or change from baseline $\geq$ 30 ms or

≥ 60 ms.
 Growth parameters, including absolute values and change from baseline in weight, height, and BMI values (converted to Z-scores and percentiles), and height velocity values and Z-scores.

Height velocity values and Z-score computations were developed with expert consultation, using normative data based on the height velocity charts of Tanner and Davies.

Additional safety analyses were performed, including summaries of selected preferred terms and clinical laboratory data, for the following areas of special safety concern associated with topiramate: growth delay/retardation, metabolic acidosis, hyperammonemia and encephalopathy, oligohydrosis and hyperthermia, renal events including nephrolithiasis, hepatic injury, and visual adverse events.

5.2 Review Strategy for Assessing Safety

Safety Review Strategy of This Reviewer

The strategy planned prior to reviewing the NDA was for the sponsor submit all types of safety data from trials planned for all indications studying topiramate. The expectation was that the adjunctive treatment experience in pediatric trials of patients (especially 2-9 years) would provide the main body of safety data relevant to the safety for pediatric patients 2-9 years who would be treated with topiramate monotherapy. However, during the review, Agency Pharmacometric reviewers noted that the pharmacokinetic (PK) exposures experienced by pediatric patients in the randomized, double-blind, placebo-controlled studies of adjunctive treatment with topiramate were generally much lower than would be experienced by younger pediatric patients (2-9 years) who would be treated with topiramate monotherapy. Considering that the sponsor had proposed monotherapy dosing from (b) (4) but that the Agency's Pharmacometric reviewers (Drs. Marathe and Yaning) had recommended monotherapy dosing for the lowest effective dose in patients 2-9 years to range from 7-13 mg/kg/day (with 13 mg/kg/day given to the youngest and 7 mg/kg/day given to the oldest of this subgroup), it was clear that the initially planned safety review strategy would not be adequate for determining the safety of monotherapy in patients 2-9 years because PK exposures in the adjunctive treatment, controlled trials were inadequate. As an additional complication, it was subsequently determined in the Agency that it would be ideal or better to recommend a range of dosing for each patient in the 2-9 year old age subgroup based upon weight. After making that determination, there was a recommended range of upper limit doses for each patient that ranged from approximately 11 – 22 mg/kg/day. Consequently, the dosing recommended by the Agency would include a lower limit target dose (7-13 mg/kg/day) and an upper limit target dose (11- 22 mg/kg/day (Table 5). With such much higher recommended dosing than had initially been planned and recommended by the sponsor (b) (4) it was clear that the originally planned strategy to rely upon safety data from randomized, double-blind, placebo-controlled studies in adjunctive therapy to support the safety of doing patient 2-9 years with monotherapy would not be reasonable/appropriate.

Table 5 **Agency Recommended Doses of Topiramate for Pediatrics by Weight in Monotherapy**

Age (years)	WT (Kg)	Dose (mg/kg/day) Lower Limit	Dose (mg/kg/day) Upper Limit	Dose (mg/day) Lower Limit	Dose (mg/day) Upper Limit
2	12.5	13.5	21.5	169	269
3.5	15	12.0	19.0	180	285
4	16	11.4	18.1	182	290
5.8	20	9.8	15.6	196	312
6	20.5	9.7	15.4	199	316
7.8	25	8.4	13.4	210	335
8	25.7	8.3	13.1	213	337
9.3	30	7.4	11.8	222	354
10	32.6	7.0	11.2	228	365

The experience in double-blind, placebo- controlled adjunctive treatment studies exposed a significant number of young pediatric patients from 2-9 years to topiramate. However, the target dose was typically ~ 6 mg/kg/day. This daily dose was much lower than the target dose of monotherapy treatment projected 7-22 mg/kg/day for patients 2-9 years based upon the Agency Pharmacometric review of this sNDA. Furthermore, many of these patients were taking one or more concomitant enzyme-inducing AEDs (EIAEDs) that can lower topiramate levels by approximately 50 %. Pharmacometrics has shown the clearance of topiramate in the adjunctive setting for patients with and without concomitant EIAEDs is greater than that the monotherapy setting, presumably due to the effect of one or more concomitant EIAEDs. Related to this, in one exploration, median Cmin in adjunctive patients of all ages (2 years – adults) was much lower than median Cmin of monotherapy patients of all ages (6 years – adults). More specifically, median Cmin in adjunctive treatment was approximately 7, 3, and 2 μg/ml in adults, patients 10-15 years, and patients 2-9 years, respectively. In contrast, median Cmin in monotherapy was approximately 8, 11, and 13 μg/ml in adults, patients 10-15 years, and patient 6-9 years, respectively, in Study 106. In addition, a relatively large number (approximately 130) of infants/toddlers (patient 1-24 months at enrollment) had been evaluated in a randomized, double-blind, placebo-controlled study of placebo and three fixed doses of topiramate (5, 15, 25 mg/kg/day) but this placebo-controlled treatment was only over 20 days. Based upon this unexpected/unanticipated pharmacokinetic (PK) difference in topiramate exposures, there was significant concern that the adjunctive, controlled treatment experience was not going to be very relevant toward assessing the safety of treating patients 2-9 years with monotherapy. Thus, limited attention was directed toward reviewing and presenting data from the placebo-controlled adjunctive treatment experience.

However, we recognized that open-label extension studies of adjunctive treatment of pediatric patients frequently used very high topiramate dosing up to 60 mg/kg/day. In view of this unexpected occurrence, the fact that pediatric monotherapy would be at least 7- 13 mg/kg/day for 2-9 year old patients, and the observation that pediatric patients 1-24 months treated with 15 mg/kg/day topiramate without an EIAED had similar Cmin to that of pediatric patients (6-9 years) who had been treated with 400 mg in the pivotal

monotherapy study, an alternative strategy was adopted for determining safety. In this alternative strategy, a conservative approach was planned and the DNP requested from the sponsor various analyses of adults (≥ 16 years) and pediatric age subgroups (< 2, 2-9, 10-15 years) for treatment-emergent adverse events (TEAEs) by dose ranges in open-label, extension, monotherapy (< 7, ≥ 7, 7-13, > 13 mg/kg/day) and in adjunctive treatment (< 15, ≥ 15, 15-30, > 30 mg/kg/day) studies (both with and without an EIAED). This approach was also "conservative" because older pediatric patients (e.g., 8 or 9 years) treated with 15 mg/kg/day would be expected to have higher topiramate levels than younger pediatric patients (e.g., 2 or 3 years) administered the same dose, 15 mg/kg/day. Furthermore, because an EIAED can decrease PK exposure of topiramate by about 50 %, the safety experience in patients treated with ≥15 mg/kg/day without an EIAED were considered to be relatively similar to that of patients treated with > 30 mg/kg/day with an EIAED. Dose-duration analyses according to these various doses and dose ranges that were also compiled. Although the pivotal, controlled trial that demonstrated efficacy and safety of topiramate monotherapy for patient 10 years and older included some patients 6-9 years, the number of these young patients was quite small (N=20 at 400 mg daily; N=17 at 50 mg daily) and only about half of these patients were at a relevant monotherapy dose. Analyses (similar to those for TEAEs) of serum bicarbonate (as a reflection of the frequency and severity of metabolic acidosis) were also subsequently requested for the open-label, monotherapy and adjunctive therapy experiences.

It is also important to note that originally, this sNDA did not contain safety data from the adjunctive treatment of infants/toddlers (1-24 months) derived from placebo-controlled and open label treatment. However, once the inadequacy of the placebo-controlled adjunctive trial experience in patients ≥ 2 years was recognized, it was also recognized that data (especially open-label, long-term treatment that involved high dosing up to 60 mg/kg/day) from treating these very young patients would be crucially important for helping support the safe treatment of 2-9 years patients with the topiramate dosing that we would be recommending for monotherapy. Despite the fact that adjunctive treatment of infants/toddlers was not approved previously because the topiramate treatment was not shown to be effective in this population, it seemed ironic that the safety experience from these very young patients treated for relatively long periods with relatively high topiramate doses under open-label conditions would be not only important but probably necessary to make a determination that monotherapy of patients 2-9 can be considered "safe." Part of the rationale for using safety data in these patients to support the safety of older patients 2-9 years was that if was "reasonably" or "adequately" safe to treat patients under 2 years with topiramate, it could be considered "safe" to treat older patients (i.e., 2- 9 years) with monotherapy as long as reasonably comparable PK exposures could be projected with treatment of the both populations for both indications.

Table 11 shows that the open-label monotherapy experience did not provide much relevant, long-term safety experience. In contrast, Table 14 for open-label, adjunctive treatment showed that there were significant numbers of pediatric patient from 1 month – 9 years who had been treated for relatively, long-term periods at topiramate doses that would be relevant (and exceeding the daily topiramate doses and PK exposures of pediatric patients 2-9 years who would be treated with topiramate monotherapy). In these analyses, 131 patients had been treated for 6 months or longer and 88 had been treated for 12 months or longer. Of interest, the overwhelming majority of these patients were in the youngest group of patients 1-24 months for which there is no approved topiramate treatment indication.

The review of all these TEAEs, SAEs, and TEAEs causing study discontinuation in these open-label studies did not reveal that there was any clear, new safety concern in patients 2-9 years that should prohibit approval of topiramate as monotherapy in this age subgroup. Overall, similar TEAEs were

observed across all age groups/subgroups. The frequencies (i.e., incidence) of TEAEs was often similar but it should be noted that the frequencies were derived from an uncontrolled, open-label treatment experience. The only type of TEAEs that seemed to be more common in pediatric patients 2-9 years appeared to be those related to various type of infections. The DNP has observed this phenomenon previously and has raised the question that topiramate (and other AEDs) may increase the risk for various types of infections in young pediatric patients. There did not appear to be a safety concern that young pediatric patients were experiencing medically serious types of TEAEs that are a focus of review in OSE. Finally, review of the various controlled studies for various indications of topiramate (at typically lower PK exposures than would be expected with monotherapy) did not reveal any clearly concerning nor unique adverse reactions other than those that have been characterized previously for topiramate treatment in its label. Although the review of open-label data for serum bicarbonate showed that the frequency and/or severity in young pediatric patients was somewhat greater than that in older pediatric patients and adults for some instances, overall, the risk for metabolic acidosis was not considered to be that different than what was already known and not sufficiently greater to preclude approval of topiramate as monotherapy in patients 2-9 years.

It is important to recognize that prior to appreciating the inadequacies of the multitude of various, safety analyses originally submitted with the NDA, my general approach of my safety review was to review various analyses of various safety parameters (e.g., TEAEs, SAEs, TEAEs causing study discontinuation, vital signs, clinical laboratory analytes, ECGs) from double-blind, controlled and open-label studies of different, topiramate treatment indications according to different doses and different ages subgroups. These analyses were for incidence, absolute central tendency over time, change from baseline for central tendency over time, and outliers and markedly abnormal outliers over time. Data were analyzed as pools when applicable and also as separate, individual studies. Despite the fact that treatment with relatively low topiramate doses (and low corresponding PK exposures) were administered in some non-epilepsy treatment indications (e.g., migraine prophylaxis), I still reviewed various data analyses from these indications not only because some studies included pediatric patients (in some cases young patients < 10 years old), but also because results of these analyses could potentially be relevant to young patients 2-9 for monotherapy if observed notable adverse reactions at relatively low topiramate dosing. My general approach particularly focused on reviewing safety analyses/results from double-blind, controlled trials for different treatment indications based upon several principles. These principles included :
1) focusing on assessing/determining treatment differences (by subtracting placebo result from result for each fixed topiramate doses when multiple, fixed doses were studied or by subtracting lowest topiramate dose such as 50 mg daily from 400 mg daily in monotherapy study 106);
2) reviewing not only pooled studies but also certain specific studies that might be of particular interest;
3) assessing the possibility of dose-response for any particular adverse reaction when possible;
4) requiring that a subgroup contain more than one TEAE of interest before considering the incidence of TEAE for that subgroup to be of interest relative to a subgroup with low incidence of 0 % TEAE, and
5) focusing on whether there were age subgroup differences in “young” pediatric patients (up to 9 years) compared to older pediatric patients (10-15 years) and also adults (≥ 16 years). Finally,

At the end of my review, I was able to conclude from these various analyses that there appears to be adequate safety to recommend topiramate approval as monotherapy for patients 2-9 years.

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable

6 Review of Efficacy

Efficacy Summary

This reviewer only conducted the safety review for this NDA and did not conduct a review for efficacy. Nevertheless, the following is a summary provided by Pharmacometrics (Drs. Anshu Marathe and Yaning Wang).

Topiramate is approved as initial monotherapy for treatment of partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in adults and children of age 10 years and above based on Phase 3 trial (study TOPMAT-EPMN-106). Topiramate is also approved as adjunctive therapy in the treatment of in adults and in children of age 2 years and above based on Phase 3 trials (studies YP, YTC and YTCE). In this application a pharmacometric bridging approach is used to gain approval for topiramate as initial monotherapy in children 2 to < 10 years of age with epilepsy, in order to meet the PREA requirements set forth in the June 29, 2005 approval letter for monotherapy treatment in adults and children of age 10 years and above. On September 29, 2006, the sponsor and FDA discussed and agreed on the pharmacometric bridging approach to address the PREA commitment. This approach was successfully used previously in the approval of Trileptal/oxcarbazepine (NDA21014-S-003) as monotherapy in pediatric subjects with epilepsy. This approach relies on matching exposures in pediatrics to exposures observed in adults to derive an optimal dose for pediatrics. This approach can be implemented if it is shown that the exposure-response relationship is similar between adults and pediatrics.

Based on the available data, it is shown that the exposure-response relationship is similar between adults and pediatrics (6-15 years) in monotherapy. Also, the exposure-response relationship is shown to be similar between adults and pediatrics (2-15 years) in adjunctive therapy. Thus, the optimal dosing regimen for pediatrics (2-9 years) in monotherapy is derived by matching exposures in pediatrics to exposures observed in adults and pediatrics (6-9 years) in TOPMAT-EPMN-106. For details of the efficacy review, see the Pharmacometrics review by Drs. Marathe and Wang.

7 Review of Safety

SAFETY SUMMARY

Safety Summary and Conclusions of Clinical Reviewer

- Overall, I can conclude that topiramate is potentially "safe" for monotherapy of pediatric patients (2-9 years) based upon my unconventional safety review and making appropriate dosing recommendations.

- My safety review was unconventional/unorthodox because my safety assessment did not involve review of empirical safety/safety data from a specific clinical trial in which 2-9 year old patients had been studied in a randomized, double-blind, controlled study for determining the efficacy and safety of the initial monotherapy for partial onset or primary generalized, tonic-clonic seizures. When initial monotherapy of epilepsy was initially approved, the approval was for treating patients 10 years and older with topiramate despite the fact that the controlled, pivotal monotherapy trials had contained younger pediatric patients 6-9 years. At the time of initial monotherapy approval, there was concern

that the safety experience was inadequate to support the safe use of monotherapy in patients 6-9 years. Consequently, the sponsor (in agreement with the DNP) planned to demonstrate the safety of topiramate as immunotherapy in patients 2-9 years based upon various pediatric safety data and corresponding analyses from other clinical trials for epilepsy and non-epilepsy indications. The expectation was that a major contribution of safety experience would be derived from adjunctive treatment of epilepsy in patients 2-9 years. However, toward the end of the initial review cycle, the Agency pharamcometric reviewers determined that the pharmacokinetic (PK) exposures of pediatric patients in the adjunctive studies were inadequate to support the safety of monotherapy of epilepsy of patients 2-9 years who would receive a lower limit, topiramate target dose of approximately 7 – 14 mg/kg/day (with mg/kg/day dosing inversely related to weight, and age for practical considerations) and an upper limit, topiramate target dose of approximately 11-22 mg/kg/day. The topiramate target dose was usually ~ 6 mg/kg/day, and often topiramate levels were significantly decreased by concomitant enzyme-inducing anti-epileptic drugs (EIAEDs) that can increase topiramate clearance (e.g., EIAEDs can decrease topiramate levels by ~ 50 %). As a result of this important, but unexpected discovery (i.e., the inadequacy of the originally submitted safety analyses to support the safety of the treatment of the indication of interest), there was a major change in the strategy of the safety review such that additional, new analyses were needed to support safety (see section 5.2 Review Strategy for Assessing Safety).

Ordinarily, a safety review/assessment depends especially upon the empirical safety experience in controlled studies in which the same indication and the same population for whom efficacy was investigated is evaluated. In contrast, my review of the safety for this indication for this population was primarily based upon imputation and many indirect inferences from other clinical safety data. There were three major categories of imputation and inferences for determining the safety of topiramate monotherapy of epilepsy for patients 2-9 years. First, the bulk of the relevant safety data supporting the safety of the indication under review was derived from topiramate treatment of a very different aged population (i.e., infants and toddlers, 1-24 months old) than the population of interest (2-9 years). Second, the bulk of the relevant safety data supporting the safety of the indication under review was derived from open-label, uncontrolled, topiramate treatment instead of from of randomized, double-blind, controlled studies. Third, the bulk of the relevant safety data supporting the safety of the indication under review was derived from a different treatment indication (adjunctive treatment of epilepsy) instead of from the indication of interest (initial monotherapy of epilepsy).

- My conclusion of the safety of treating patients 2-9 years with topiramate as initial monotherapy relied on the perspective that "young" pediatric patients 2-9 years and infants/toddlers ($\leq$ 2 years) treated with "high" dosing topiramate in open-label setting did not seem to experience unique treatment-emergent adverse events (TEAEs) compared to those experienced by older pediatric patients or adults. In particular, there did not appear to be any unique, medically serious adverse events experienced by young patients relative to the safety profile in the topiramate label. Although some of these TEAEs appeared to occur more frequently in younger pediatric patients than in older patients, these TEAEs did not seem uniquely severe in younger pts compared to older pts. Neither did they clearly appear to occur in a tremendously greater frequency in young pediatric patients 2-9 years than in than older patients during open-label treatment. I also thought that if treatment with relatively high doses of topiramate were reasonably "safe" and tolerated in very young pediatric patients (i.e., infants and toddlers 1-24 months), who were presumably exposed to topiramate levels that were as high (and possibly even higher because of decreased topiramate clearance in patients 1-24 months compared to pediatric patients $\geq$ 2 years), that similar treatment of older pediatric patients 2-9 years would be reasonably "safe" and tolerated.

- I also conclude that the dosing of topiramate as monotherapy in patients 2-9 years is reasonably "safe" because it involves slow titration of topiramate to a lower limit target dose and gradual titration to a higher dose (not to exceed the upper limit target in the label) if there is inadequate seizure control.

SPONSOR'S EXECUTIVE SUMMARY OF CLINICAL SAFETY

This summary document supports the safety profile of topiramate monotherapy in children ages 2 to 9 years with partial onset seizures (POS) and primary generalized tonic-clonic (PGTC) seizures. Integrated data are presented from clinical studies conducted in adult and pediatric subjects.

As requested by the Food and Drug Administration (FDA) at the 19 September 2006 meeting (Mod 1.6.3\FDA Meeting Minutes September 2006), safety analyses are presented by age subgroup from both individual and pooled studies in 4 therapeutic indications that enrolled pediatric subjects ≥ 2 years old: epilepsy adjunctive therapy, epilepsy monotherapy, migraine prophylaxis, and bipolar disorder. Additional guidance was received during the Type C General Guidance meeting on 27 February 2008 and in follow-up comments from FDA dated 29 August 2008 (Mod 1.6.3).

Safety and related information are presented for 6,654 subjects treated with topiramate in 62 clinical trials (8,500 subject-years of exposure), including 573 pediatric subjects aged 2 to 9 years, 778 pediatric subjects aged 10 to 15 years, and 5,303 adult subjects aged 16 and older (subject ages are those at enrollment).

Overall, the AE profile for topiramate was comparable across age groups, and the higher frequency of some events among those aged 2-9, such as respiratory and infection-related AEs, is consistent with the incidence among placebo-treated subjects aged 2-9 from the double-blind epilepsy adjunctive studies. The frequencies and types of serious adverse events reported for subjects aged 2-9 were consistent with the established safety profile of topiramate.

Also consistent with the known safety profile of topiramate, a decrease from baseline in serum bicarbonate values and an increase in serum chloride values were observed. While the incidence of bicarbonate values <17 mmol/L was generally higher in topiramate-treated subjects aged 2-9 compared with those 10-15 and ≥ 16, it was rarely associated with acidosis-related clinical signs/symptoms reported as AEs among subjects aged 2-9. There were no other notable laboratory findings among subjects aged 2-9, nor were there any remarkable findings for the 2-9 age group in ECG parameters or vital signs measurements.

Across indications, anorexia and weight decreased were the only growth-related adverse events reported for subjects aged 2-9, and these events were rarely treatment limiting. Over the entire course of topiramate treatment (combined double-blind and open-label phases), 15% of those aged 6-9 in the epilepsy monotherapy studies had weight Z-score reductions of ≥ 1 and 4% had height Z-score reductions of ≥ 1; in the epilepsy adjunctive studies, 24% of those aged 2-9 had weight Z-score reductions of ≥ 1 and 4% had height Z-score reductions of ≥ 1. Height velocity analyses suggest that subjects aged 2-9 who received topiramate as adjunctive therapy or monotherapy for epilepsy tended to grow at a slower rate than did age-matched average-maturing children. However, when interpreting these data, consideration must be given to the limitations of the available data set as well as to those of the novel statistical methodology utilized.

In summary, the safety profile of topiramate in subjects aged 2-9, including the types and frequencies of adverse events and laboratory abnormalities, was generally consistent with that of older pediatric and adult subjects. Taken together these data support the safe use of topiramate as monotherapy in subjects with epilepsy aged 2-9 years, under the proposed dosing recommendations.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.1.

7.1.2 Categorization of Adverse Events

Standard approaches for categorizing adverse events were used.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See section 5.1.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics

The median final daily dosage and the median maximum daily dosage of topiramate were consistent with the corresponding target dosages in each of the treatment groups (Table 6) for Study 106, the key pivotal study that supported approval of monotherapy in patients 10 and older.

Per protocol, dose reductions were allowed for subjects who had difficulty reaching or maintaining their assigned dose or the maximum tolerated dose; following dose reductions during the stabilization period, the topiramate dose was not to be increased again. Dosage reductions or temporary interruptions of study medication due to adverse events occurred in 56 subjects (24%) in topiramate 400 mg/day group and 20 subjects (9%) in topiramate 50 mg/day group. Thus, the mean (SD) average daily dosages in each of the treatment groups were lower than the assigned dosages, namely, 42.5 (8.95) mg/day in topiramate 50 mg/day treatment group and 275.3 (120.97) mg/day in topiramate 400 mg/day treatment group.

In the pivotal study EPMN-106, the two treatment groups included 50 or 400 mg/day topiramate as target maintenance dosages. Only 58% of patients achieved 400 mg/day as maintenance dose. Patients were allowed dose reductions after day 22 during the study. Mean (±SD) maintenance dosages were 43± 14 mg/day in the 50 mg group and 309± 129mg/day in the 400 mg group, of which 58% were maintained on the target dose. The most common dose-related adverse events were paresthesia, weight loss, and decreased appetite. Discontinuations due to cognitive-related adverse events were 2% in the 50 mg group and 7% in the 400 mg group. More patients randomized to the 400 mg dose group had treatment-limiting events compared to the lower dose; overall 7% and 19%, respectively discontinued with adverse events

during the median treatment duration of 9 months. CNS events were the most common adverse events leading to discontinuation, dose reductions, or temporary interruptions of therapy. In most patients (50 mg, 2/5; 400 mg 10/16), treatment limiting cognitive effects emerged during the 3 week titration period in which dosage reductions were not allowed. Among patients with any adverse event, the dose was reduced or therapy temporarily interrupted in 9% of the patients in the 50 mg group and 24% in the 400 mg group. When therapy could be adjusted to manage adverse events, 70% of patients completed the study.

Table 6 Daily Dosage of Topiramate (ITT Population; Study TOPMAT-EPMN-106

	TPM 50 (N=234)	TPM 400 (N=236)
Average Daily Dose (mg/day)		
Mean	42.5	275.3
SD	8.95	120.97
Median	47.5	335.3
Range	17.0 - 61.7	27.4 - 399.1
Maximum Daily Dose (mg/day)		
Mean	48.5	339.7
SD	9.43	121.42
Median	50.0	400.0
Range	25.0 - 100.0	50.0 - 800.0
Final Daily Dose (mg/day)		
Mean	42.8	309.4
SD	14.07	128.90
Median	50.0	400.0
Range	0.0 - 50.0	0.0 - 450.0

Cross-reference: Attachment 4.1.1

The majority of those subjects who completed the double-blind phase of the study at the time of its termination in each of the 2 groups achieved their target dosage (92% in the topiramate 50 mg/day group and 71% in the topiramate 400 mg/day group). Less than one-half of the subjects who withdrew from the study in either of the 2 groups (49% in topiramate 50 mg/day group and 43% in topiramate 400 mg/day group) had reached their target dosage at the time of withdrawal.

By design, the duration of the double-blind phase could vary. Subjects who neither experienced a first seizure nor withdrew from the study were to receive the double-blind treatment until 6 months after the last subject was randomized. A total of 217 subjects (46% of the intent-to-treat population) completed the double-blind phase of the study at the time of its termination. The cumulative distribution of subjects by duration of therapy in the range from at least 1 day to more than 630 days is presented in Table 7. The median duration of exposure for all subjects in the intent-to-treat population was approximately 9 months (266 days; range, 9 to 786 days).

Of the 470 subjects in the intent-to-treat population, 294 (63%) received the double-blind study medication for at least 6 months, and approximately one-third (166 subjects; 35%) were treated for at least 360 days.

Table 7 **Cumulative Distribution of Subjects by Duration of Therapy (ITT Population ; Study TOPMAT-EPMN-106)**

Duration of Therapy	TPM 50		TPM 400		Total	
(Days)	N	%	n	%	N	%
≥ 1	234	100	236	100	470	100
≥ 15	225	96	224	95	449	96
≥ 30	204	87	203	86	407	87
≥ 90	159	68	171	72	330	70
≥180	145	62	149	63	294	63
≥270	115	49	117	50	232	49
≥360	79	34	87	37	166	35
≥450	58	25	67	28	125	27
≥540	33	14	33	14	66	14
> 630	13	6	13	6	26	6
N	234		236		470	
Mean	276.0		287.4		281.7	
SD	208.92		214.87		211.78	
Median	266.0		266.5		266.0	
Range	9 – 763		9 - 786		9 - 786	

Cross-reference: Attachment 4.2

7.2.2 Target Populations

Topiramate Treatment as Monotherapy

The following Table 8 shows the dose-duration exposure of various age groups in the key monotherapy Study 106 that demonstrated efficacy for patient 10 years and older. **It is important to recognize that these dose-durations tables (provided by the sponsor) present results for each duration as a mutually exclusive cell and do not show cumulative duration of treatment exposure for a certain dose. To determine the cumulative duration of exposure to a certain dose/dose range, one would simply need to add the number of patients who had exposure to the shortest duration of interest to the remaining patients who were exposed to the same dose/dose range for all longer treatment durations.** Dose-duration data from other pivotal, monotherapy studies are not shown because the highest, randomized daily topiramate dose in these studies was 200 mg (lower than the DNP recommended lower limit target daily doses for patients 2-9 years.

Table 9 shows the dose-durations results for Study 106 for the combined treatment experience in the double-blind and the open-label phase of study.

Table 10 shows the dose-duration results for the open-label monotherapy treatment with topiramate in the extension phase of double-blind, pivotal trials. The dose ranges shown (< 7, ≥ 7, 7-13, > 13 mg/kg/day)

Table 8 Topiramate Dose-Duration (NOT CUMULATIVE) Exposures in Double-Blind Study 106: Treatment Duration by Randomized Dose and Age

	TPM 50 mg/day					TPM 400 mg/day				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
TREATMENT DURATION, DAYS										
N	17	57	160	74	234	20	57	159	77	236
Category, n (%)										
1-179 DAYS (<6 MONTHS)	5 (29)	13 (23)	70 (44)	18 (24)	88 (38)	7 (35)	7 (12)	72 (45)	14 (18)	86 (36)
180-359 DAYS (6 MONTHS - <1 YEAR)	5 (29)	19 (33)	43 (27)	24 (32)	67 (29)	5 (25)	19 (33)	38 (24)	24 (31)	62 (26)
360-539 DAYS (1 YEAR - <1.5 YEARS)	4 (24)	19 (33)	23 (14)	23 (31)	46 (20)	6 (30)	21 (37)	28 (18)	27 (35)	55 (23)
540-719 DAYS (1.5 YEARS - <2 YEARS)	3 (18)	6 (11)	20 (13)	9 (12)	29 (12)	2 (10)	10 (18)	14 (9)	12 (16)	26 (11)
720-1079 DAYS (2 YEARS - <3 YEARS)	0	0	4 (3)	0	4 (2)	0	0	7 (4)	0	7 (3)
Mean	328.4	316.2	259.1	319.0	278.0	291.9	371.4	260.4	350.8	289.9
SD	195.02	180.48	216.94	182.62	208.19	204.37	172.49	222.03	183.29	214.04
Median	353.0	322.0	230.0	332.5	266.0	231.0	383.0	197.0	365.0	270.0
Minimum	30	9	9	9	9	12	29	9	12	9
Maximum	648	691	763	691	763	627	627	786	627	786
Total Exposure (subject years)	15.3	49.3	113.5	64.6	178.1	16.0	58.0	113.4	73.9	187.3

Table 9 Topiramate Treatment Duration (NOT CUMULATIVE) : Summary for the Combined Double-Blind and Open-Label Phases of the Epilepsy Monotherapy Studies

	Total TPM				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
TREATMENT DURATION, DAYS					
N	67	178	882	245	1127
Category, n (%)					
1-179 DAYS (<6 MONTHS)	13 (19)	23 (13)	298 (34)	36 (15)	334 (30)
180-359 DAYS (6 MONTHS - <1 YEAR)	9 (13)	33 (19)	164 (19)	42 (17)	206 (18)
360-539 DAYS (1 YEAR - <1.5 YEARS)	7 (10)	16 (9)	129 (15)	23 (9)	152 (13)
540-719 DAYS (1.5 YEARS - <2 YEARS)	5 (7)	18 (10)	63 (7)	23 (9)	86 (8)
720-1079 DAYS (2 YEARS - <3 YEARS)	23 (34)	66 (37)	126 (14)	89 (36)	215 (19)
1080-1439 DAYS (3 YEARS - <4 YEARS)	5 (7)	20 (11)	53 (6)	25 (10)	78 (7)
1440-1799 DAYS (4 YEARS - <5 YEARS)	1 (1)	1 (1)	10 (1)	2 (1)	12 (1)
1800-2159 DAYS (5 YEARS - <6 YEARS)	3 (4)	1 (1)	7 (1)	4 (2)	11 (1)
2160 DAYS OR MORE (>=6 YEARS)	1 (1)	0	32 (4)	1 (<1)	33 (3)
Mean	676.7	653.3	501.5	659.7	535.9
SD	513.51	393.36	543.13	428.58	524.28
Median	714.0	706.0	315.5	714.0	377.0
Minimum	12	16	3	12	3
Maximum	2350	2071	2716	2350	2716
Total Exposure (subject years)	124.1	318.4	1211.0	442.5	1653.5

Table 10 Monotherapy Open-Label Extension Trials: Treatment Duration (NOT CUMULATIVE) by Modal Dose and Age

Modal Dose (mg/kg/day)	< 7				≥ 7			
Age (years)	6-9	10-15	6-15	≥ 16	6-9	10-15	6-15	≥ 16
N	16	43	59	268	25	69	94	79
Trt Dur (Days), n (%)								
1-179 (<6 mos)	3 (19)	4 (9)	7 (12)	59 (22)	1 (4)	4 (6)	5 (5)	17 (22)
180-359 (6 mos - <1 yr)	2 (13)	6 (14)	8 (14)	29 (11)	5 (20)	9 (13)	14 (15)	7 (9)
360-539 (1 yr - <1.5 yrs)	5 (31)	13 (30)	18 (31)	35 (13)	5 (20)	12 (17)	17 (18)	5 (6)
540-719 (1.5 yrs - <2 yrs)	2 (13)	11 (26)	13 (22)	68 (25)	11 (44)	37 (54)	48 (51)	23 (29)
720-1079 (2 yrs - <3 yrs)	1 (6)	7 (16)	8 (14)	34 (13)	1 (4)	6 (9)	7 (7)	12 (15)
1080-1439 (3 yrs - <4 yrs)	0	2 (5)	2 (3)	12 (4)	1 (4)	0	1 (1)	5 (6)
1440-1799 (4 yrs - <5 yrs)	2 (13)	0	2 (3)	7 (3)	1 (4)	0	1 (1)	2 (3)
1800-2159 (5 yrs - <6 yrs)	0	0	0	16 (6)	0	1 (1)	1 (1)	5 (6)
≥ 2160 (≥ 6 yrs)	1 (6)	0	1 (2)	8 (3)	0	0	0	3 (4)
Mean	640.3	537.8	565.6	654.2	579.1	538.9	549.6	725.1
SD	648.04	292.08	415.33	591.74	339.4	261.17	282.7	626.79
Median	424	470	434	562	569	576	573	588
Minimum	47	100	47	1	168	22	22	5
Maximum	2300	1418	2300	2556	1715	1988	1988	2486
Total Exposure (Subj Yrs)	28	63.3	91.4	480	39.6	101.8	141.4	156.8

Modal Dose (mg/kg/day)	7- 13				> 13			
Age (years)	6-9	10-15	6-15	≥ 16	6-9	10-15	6-15	≥ 16
N	15	62	77	75	10	7	17	4
Trt Dur (Days), n (%)								
1-179 (<6 mos)	1 (7)	4 (6)	5 (6)	17 (23)	0	0	0	0
180-359 (6 mos - <1 yr)	3 (20)	9 (15)	12 (16)	7 (9)	2 (20)	0	2 (12)	0
360-539 (1 yr - <1.5 yrs)	3 (20)	12 (19)	15 (19)	5 (7)	2 (20)	0	2 (12)	0
540-719 (1.5 yrs - <2 yrs)	5 (33)	31 (50)	36 (47)	22 (29)	6 (60)	6 (86)	12 (71)	1 (25)
720-1079 (2 yrs - <3 yrs)	1 (7)	6 (10)	7 (9)	11 (15)	0	0	0	1 (25)
1080-1439 (3 yrs - <4 yrs)	1 (7)	0	1 (1)	4 (5)	0	0	0	1 (25)
1440-1799 (4 yrs - <5 yrs)	1 (7)	0	1 (1)	2 (3)	0	0	0	0
1800-2159 (5 yrs - <6 yrs)	0	0	0	4 (5)	0	1 (14)	1 (6)	1 (25)
≥ 2160 (≥ 6 yrs)	0	0	0	3 (4)	0	0	0	0
Mean	619.1	506	528.1	696.6	519.1	829.7	647	1259
SD	428.5	198.3	259.65	618.03	122.1	513.21	363.3	626.46
Median	568	568	568	583	577	681	588	1134.5
Minimum	168	22	22	5	259	584	259	689
Maximum	1715	1064	1715	2486	605	1988	1988	2078
Total Exposure (Subj Yrs)	25.4	85.9	111.3	143	14.2	15.9	30.1	13.8

Table 11 Topiramate Modal Dose and Open-Label Treatment CUMULATIVE Duration of Pediatric Patients During Topiramate Monotherapy Treatment of Epilepsy

	6 – 9 yo	10 – 15 yo
Any TPM Modal Dose		
N	41	112
≥ 6 months	37	104
≥ 12 months	30	89
TPM Modal Dose < 7 mg/kg/day		
N	16	43
≥ 6 months	13	39
≥ 12 months	11	33
TPM Modal Dose ≥ 7 mg/kg/day		
N	25	69
≥ 6 months	24	65
≥ 12 months	19	56
TPM Modal Dose 7 - 13 mg/kg/day		
N	15	62
≥ 6 months	14	58
≥ 12 months	11	49
Modal Dose > 13 mg/kg/day		
N	10	7
≥ 6 months	10	7
≥ 12 months	8	7

focus on the results for patients 6-9 and 10-15 years old to show the numbers treated for at least 6 or 12 months. These dose ranges were selected because the Pharmacometric analysis, that sought to match a Cmin exposure in adults, determined that the dose range for patients 2-9 years old range between 7-13 mg/kg/day with the youngest patients targeted for the highest dose. The expectation was that all patients would achieve a median Cmin of ~ 8 µg/ml. This Cmin in adults was primarily determined from population pharmacokinetic (PK) analyses in which most patients (N=138) had PK samples at various times after dosing and a relatively small percentage (~ 25 %) of adults had actual Cmin sampling for which the median Cmin was approximately 11 µg/ml.

Table 11 summarizes the **cumulative** duration of treatment for the most important and relevant modal dose range results from Table 10 and focuses on results for patients 6-9 and 10-15 years.

Reviewer Comment

- Table 8 shows that a very small number of only 20 patients 6-9 years were randomized to a 400 mg daily topiramate dos and treated in the randomized, double-blind, phase of Study 106. Of these 20 patients, only 13 were treated for at least 6 months and only 8 were treated for at least 12 months. Such low numbers for a relevant daily dose are not helpful in supporting a long-term safety experience.

- Table 9 shows the dose-duration results in Study 106 for the double, blind and open-label phases of Study 106 but only in terms of any topiramate dose and not relative to "high" topiramate dosing that would be relevant to the topiramate exposures for patients 2-9 years treated as monotherapy. Although 54 patients were treated for 6 months or longer and 45 patients were treated for 12 months or longer, it is not possible to attribute any significance to these numbers of patients without knowing the daily dosing exposures that these patients experienced.

- Table 10 and Table 11 shows the dose-duration results for topiramate**, open-label treatment as monotherapy** according to different modal dose ranges (mg/kg/day basis) and different age subgroups. Initially, the Pharmacometric reviewers had recommended topiramate dosing between 7-13 mg/kg/day for patients 2-9 years with the highest dose recommended in the youngest patients and the lowest dose recommended in the oldest patients. The expectation was that all these patients would/might achieve similar Cmin levels because oral topiramate clearance is increased in younger pediatric patients. However, the numbers of patients in the relevant age group 2-9 years who were treated for 6 months or longer are still quite small. At a somewhat relevant dose of ≥ 7 mg/kg/day, only 24 patients were treated for at least 6 months and only 19 were treated for at least 12 months. At a greater modal dose (> 13 mg/kg/day), only 10 patients were treated for at least 6 months and only 8 were treated for at least 12 months. Even if one looks at the treatment experience in the 7-13 range, the numbers of patients are still very small (N=14 for at least 6 months; N=11 for at least 12 months)

Topiramate Treatment as Adjunctive Therapy

Initially, the adjunctive treatment experience in pediatric patients (especially 2-9 years) was expected to support the safety of treating this same age range of patients with topiramate as monotherapy. However, it has been noted that the randomized, double-blind, placebo-controlled, adjunctive study experience was not very relevant to the exposures expected with monotherapy. Neither was the monotherapy safety experience adequate in terms of the numbers of patients below 10 years who had been treated with topiramate. **Therefore, exploratory analyses were conducted in open-label adjunctive studies to examine the dose-duration results for various dose ranges including relatively high dose ranges that could have relevance to the young patients (2-9 years) who might be treated with monotherapy.**

It is important to recognize that these dose-durations tables (provided by the sponsor) present results for each duration as a mutually exclusive cell and do not show cumulative duration of treatment exposure for a certain dose. The cumulative duration of exposure to a certain dose/dose range can be determined by adding the number of patients who had exposure to the shortest treatment duration of interest to the remaining patients who were exposed to the same dose/dose range for all longer treatment durations.

A significant body of data was also available from adjunctive treatment of partial seizures in very young pediatric patients (1-24 months). These data had not been submitted with this NDA because it was not thought that these data would be relevant considering that these patients were younger than the population for which the current NDA was seeking approval). The sponsor had previously submitted these infant/toddler data in an NDA as part of a Pediatric Written Request (PWR). Although the sponsor did not obtain approval for treating these patient s because the randomized, double-blind, placebo-controlled study of efficacy did not suggest efficacy, the sponsor did receive pediatric exclusivity because it met the provisions of the PWR. Of interest, in the investigation of these very young patients with topiramate, approximately 280 patients had been treated with topiramate with very high doses (up to 60 mg/kg/day) in a long-term extension study for up to 1 year.

This clinical development program in infants/toddlers had also studied topiramate PK in these patients and found that a topiramate dose of 15 mg/kg/day (without concomitant enzyme-inducing AED – EIAED) resulted in a mean Cmin of ~ 13 μg/ml. This level was similar to the level of topiramate observed in 19 patients who were 6-9 years old and had been participated in the randomized, double-blind phase of Study 106 for monotherapy. In view of this observation and the

fact that the highest dose of topiramate initially projected for monotherapy in young patients 2-9 years was ~ 13 mg/kg/day, and the observation that a concomitant EIAED decreases topiramate levels by approximately 50 %, it was decided that dose-duration and TEAE analyses would be conducted in open-label studies not only for various age subgroups but also for various, potentially relevant topiramate modal dose ranges (< 15, ≥ 15, 15-30, and > 30 mg/kg/day), and also according to whether a concomitant EIAED was used. Thus, the open-label, adjunctive analyses

Table 12 and Table 13 show results of dose-duration analyses in open-label, adjunctive, extension trials according to various topiramate dose ranges (< 15, ≥ 15, 15-30, and > 30 mg/kg/day) outlined above here, various age subgroups, various durations of topiramate treatment, and whether or not . These results are for patients who were taking at least one concomitant AED that was not an EIAED.

Table 14 summarizes dose-duration results for all the various pediatric age subgroups according to the dose ranges outline for patients taking any concomitant AED, for patients not taking an EIAED, and for patients taking at least one concomitant EIAED. Table 15 summarizes what are believed to be the most relevant results for the ≤ 2 yo subgroup, the 2-9 yo subgroup, and all of these young patients combined (≤ 9 yo) and shows ≥ 6 and ≥ 12 month exposures for patients who were treated with a modal topiramate dose of ≥ 15 mg/kg/day without any EIAED and for patients who were treated with a modal topiramate dose of > 30 mg/kg/day with at least one EIAED.

Table 12 Adjunctive Treatment of Epilepsy Open-Label Extension Trials: Treatment Duration (NOT CUMULATIVE) by Modal Dose and Age for Subjects NOT Taking Concomitant EIAED

Modal Dose (mg/kg/day)	<15							≥ 15						
Age (years)	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16
N	23	110	125	235	138	263	648	81	11	21	32	14	35	74
Trt Dur (Days), n (%)														
1-179 (<6 mos)	8 (35)	45 (41)	44 (35)	89 (38)	33 (24)	77 (29)	213 (33)	21 (26)	1 (9)	3 (14)	4 (13)	0	3 (9)	7 (9)
180-359 (6 mos - <1 yr)	5 (22)	39 (35)	40 (32)	79 (34)	44 (32)	84 (32)	128 (20)	23 (28)	2 (18)	4 (19)	6 (19)	2 (14)	6 (17)	11 (15)
360-539 (1 yr - <1.5 yrs)	10 (43)	10 (9)	19 (15)	29 (12)	19 (14)	38 (14)	111 (17)	37 (46)	0	3 (14)	3 (9)	0	3 (9)	7 (9)
540-719 (1.5 yrs - <2 yrs)	0	6 (5)	2 (2)	8 (3)	8 (6)	10 (4)	53 (8)	0	1 (9)	3 (14)	4 (13)	1 (7)	4 (11)	9 (12)
720-1079 (2 yrs - <3 yrs)	0	1 (1)	5 (4)	6 (3)	16 (12)	21 (8)	67 (10)	0	3 (27)	2 (10)	5 (16)	1 (7)	3 (9)	11 (15)
1080-1439 (3 yrs - <4 yrs)	0	3 (3)	3 (2)	6 (3)	5 (4)	8 (3)	34 (5)	0	0	2 (10)	2 (6)	1 (7)	3 (9)	9 (12)
1440-1799 (4 yrs - <5 yrs)	0	3 (3)	4 (3)	7 (3)	4 (3)	8 (3)	24 (4)	0	2 (18)	2 (10)	4 (13)	2 (14)	4 (11)	13 (18)
1800-2159 (5 yrs - <6 yrs)	0	2 (2)	4 (3)	6 (3)	7 (5)	11 (4)	9 (1)	0	0	2 (10)	2 (6)	3 (21)	5 (14)	3 (4)
≥ 2160 (≥ 6 yrs)	0	1 (1)	4 (3)	5 (2)	2 (1)	6 (2)	9 (1)	0	2 (18)	0	2 (6)	4 (29)	4 (11)	4 (5)
Mean	256.7	348.5	444.6	399.6	533.1	491	481.8	285.3	1076.1	770.4	875.5	1573.1	1091.5	934.5
SD	136.87	479.53	577.83	535.12	556.26	567.26	507.28	109.92	811.94	643.99	708.51	794.3	802.73	633.86
Median	351	186.5	199	190	325	274	335.5	356	829	558	602.5	1789	826	800
Minimum	10	1	18	1	4	4	1	28	126	140	126	303	140	31
Maximum	394	3256	2799	3256	3247	3247	2855	402	2449	2084	2449	2769	2769	2679
Total Exposure (Subj Yrs)	16.2	104.9	152.2	257.1	201.4	353.6	854.9	63.3	32.4	44.3	76.7	60.3	104.6	189.3

Modal Dose (mg/kg/day)	15 - 30							> 30						
Age (years)	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16
N	46	9	21	30	13	34	68	35	2	0	2	1	1	6
Trt Dur (Days), n (%)														
1-179 (<6 mos)	17 (37)	1 (11)	3 (14)	4 (13)	0	3 (9)	6 (9)	4 (11)	0	0	0	0	0	1 (17)
180-359 (6 mos - <1 yr)	11 (24)	2 (22)	4 (19)	6 (20)	2 (15)	6 (18)	11 (16)	12 (34)	0	0	0	0	0	0
360-539 (1 yr - <1.5 yrs)	18 (39)	0	3 (14)	3 (10)	0	3 (9)	7 (10)	19 (54)	0	0	0	0	0	0
540-719 (1.5 yrs - <2 yrs)	0	1 (11)	3 (14)	4 (13)	0	3 (9)	7 (10)	0	0	0	0	1 (100)	1 (100)	2 (33)
720-1079 (2 yrs - <3 yrs)	0	1 (11)	2 (10)	3 (10)	1 (8)	3 (9)	10 (15)	0	2 (100)	0	2 (100)	0	0	1 (17)
1080-1439 (3 yrs - <4 yrs)	0	0	2 (10)	2 (7)	1 (8)	3 (9)	9 (13)	0	0	0	0	0	0	0
1440-1799 (4 yrs - <5 yrs)	0	2 (22)	2 (10)	4 (13)	2 (15)	4 (12)	11 (16)	0	0	0	0	0	0	2 (33)
1800-2159 (5 yrs - <6 yrs)	0	0	2 (10)	2 (7)	3 (23)	5 (15)	3 (4)	0	0	0	0	0	0	0
≥ 2160 (≥ 6 yrs)	0	2 (22)	0	2 (7)	4 (31)	4 (12)	4 (6)	0	0	0	0	0	0	0
Mean	262.1	1132.8	770.4	879.1	1645.4	1105	935.4	315.8	821		821	634	634	924.5
SD	119.99	896.74	643.99	732.38	777.39	810.79	644.62	87.67	11.31		11.31			545.48
Median	319.5	879	558	588	1807	846.5	800	362	821		821	634	634	802
Minimum	28	126	140	126	303	140	31	48	813		813	634	634	164
Maximum	402	2449	2084	2449	2769	2769	2679	393	829		829	634	634	1577
Total Exposure (Subj Yrs)	33	27.9	44.3	72.2	58.6	102.9	174.2	30.3	4.5		4.5	1.7	1.7	15.2

Modal dose is based on open-label exposure.EIAED = Enzyme-Inducing Anti-Epileptic Drug.
Trials included in data summaries: ABS-001, COGF-001, EPAJ-111, EPPD-001, EPPD-002, IP, M215, M216, M218, MET-001, MS220, YEP, YET, YC, YH, YI, YJ, YK, YKE, YKP, YKT, YLT, YLTE, YOL, YOLE, YZ YZW, OL extension of YF, YG, YP, YTC, YTCE, YL. TOPMAT-EPMN-1002 and TOPMAT-EPMN-3001.

Table 13 Adjunctive Treatment of Epilepsy Open-Label Extension Trials: Treatment Duration (NOT CUMULATIVE) by Modal Dose and Age for Subjects Taking Concomitant EIAED

Modal Dose (mg/kg/day)	<15							≥ 15						
Age (years)	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16
N	55	64	96	160	184	280	1910	125	13	13	26	29	42	277
Trt Dur (Days), n (%)														
1-179 (<6 mos)	23 (42)	17 (27)	23 (24)	40 (25)	49 (27)	72 (26)	520 (27)	28 (22)	1 (8)	0	1 (4)	5 (17)	5 (12)	19 (7)
180-359 (6 mos - <1 yr)	17 (31)	21 (33)	38 (40)	59 (37)	53 (29)	91 (33)	384 (20)	32 (26)	2 (15)	2 (15)	4 (15)	3 (10)	5 (12)	55 (20)
360-539 (1 yr - <1.5 yrs)	15 (27)	9 (14)	11 (11)	20 (13)	17 (9)	28 (10)	283 (15)	65 (52)	3 (23)	0	3 (12)	2 (7)	2 (5)	59 (21)
540-719 (1.5 yrs - <2 yrs)	0	3 (5)	3 (3)	6 (4)	16 (9)	19 (7)	199 (10)	0	4 (31)	1 (8)	5 (19)	2 (7)	3 (7)	26 (9)
720-1079 (2 yrs - <3 yrs)	0	6 (9)	10 (10)	16 (10)	23 (13)	33 (12)	206 (11)	0	0	3 (23)	3 (12)	6 (21)	9 (21)	42 (15)
1080-1439 (3 yrs - <4 yrs)	0	4 (6)	3 (3)	7 (4)	11 (6)	14 (5)	135 (7)	0	2 (15)	3 (23)	5 (19)	3 (10)	6 (14)	27 (10)
1440-1799 (4 yrs - <5 yrs)	0	3 (5)	4 (4)	7 (4)	8 (4)	12 (4)	86 (5)	0	0	2 (15)	2 (8)	4 (14)	6 (14)	35 (13)
1800-2159 (5 yrs - <6 yrs)	0	0	1 (1)	1 (1)	0	1 (0)	48 (3)	0	1 (8)	1 (8)	2 (8)	1 (3)	2 (5)	8 (3)
≥ 2160 (≥ 6 yrs)	0	1 (2)	3 (3)	4 (3)	7 (4)	10 (4)	49 (3)	0	0	1 (8)	1 (4)	3 (10)	4 (10)	6 (2)
Mean	213.8	467	478.7	474	546.9	523.6	577.9	290.2	704.2	1114.4	909.3	996.3	1032.9	778.3
SD	148.74	467.81	506.59	489.98	571.87	550.41	578.27	112.35	539.25	630.19	611.52	820.96	761.29	557.46
Median	275	293.5	296	294.5	322.5	310	379	360	548	1095	727.5	828	835.5	559
Minimum	7	2	32	2	18	18	1	27	176	286	176	70	70	49
Maximum	395	2311	2424	2424	3218	3218	3261	407	2109	2339	2339	3266	3266	2525
Total Exposure (Subj Yrs)	32.2	81.8	125.8	207.6	275.5	401.4	3021.9	99.3	25.1	39.7	64.7	79.1	118.8	590.3

Modal Dose (mg/kg/day)	15 - 30							> 30						
Age (years)	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16	≤ 2	2-5	6-9	2-9	10-15	6-15	≥ 16
N	80	11	12	23	27	39	259	45	2	1	3	2	3	18
Trt Dur (Days), n (%)														
1-179 (<6 mos)	23 (29)	1 (9)	0	1 (4)	4 (15)	4 (10)	19 (7)	5 (11)	0	0	0	1 (50)	1 (33)	0
180-359 (6 mos - <1 yr)	18 (23)	2 (18)	2 (17)	4 (17)	3 (11)	5 (13)	52 (20)	14 (31)	0	0	0	0	0	3 (17)
360-539 (1 yr - <1.5 yrs)	39 (49)	2 (18)	0	2 (9)	2 (7)	2 (5)	53 (20)	26 (58)	1 (50)	0	1 (33)	0	0	6 (33)
540-719 (1.5 yrs - <2 yrs)	0	4 (36)	1 (8)	5 (22)	2 (7)	3 (8)	25 (10)	0	0	0	0	0	0	1 (6)
720-1079 (2 yrs - <3 yrs)	0	0	3 (25)	3 (13)	5 (19)	8 (21)	38 (15)	0	0	0	0	1 (50)	1 (33)	4 (22)
1080-1439 (3 yrs - <4 yrs)	0	2 (18)	3 (25)	5 (22)	3 (11)	6 (15)	25 (10)	0	0	0	0	0	0	2 (11)
1440-1799 (4 yrs - <5 yrs)	0	0	1 (8)	1 (4)	4 (15)	5 (13)	33 (13)	0	0	1 (100)	1 (33)	0	1 (33)	2 (11)
1800-2159 (5 yrs - <6 yrs)	0	0	1 (8)	1 (4)	1 (4)	2 (5)	8 (3)	0	1 (50)	0	1 (33)	0	0	0
≥ 2160 (≥ 6 yrs)	0	0	1 (8)	1 (4)	3 (11)	4 (10)	6 (2)	0	0	0	0	0	0	0
Mean	271	593.5	1077.6	846	1036.9	1049.4	783	324.2	1313	1556	1394	449	818	711.2
SD	122.74	366.89	643.45	573.88	830.68	769.63	565.87	81.71	1125.71		808.27	535.99	743.05	424.99
Median	355.5	548	945	710	843	843	559	365	1313	1556	1556	449	828	550.5
Minimum	27	176	286	176	104	104	49	54	517	1556	517	70	70	269
Maximum	407	1281	2339	2339	3266	3266	2525	392	2109	1556	2109	828	1556	1580
Total Exposure (Subj Yrs)	59.4	17.9	35.4	53.3	76.6	112	555.2	39.9	7.2	4.3	11.4	2.5	6.7	35

Modal dose is based on open-label exposure. EIAED = Enzyme-Inducing Anti-Epileptic Drug.
Trials included in data summaries: ABS-001, COGF-001, EPAJ-111, EPPD-001, EPPD-002, IP, M215, M216, M218, MET-001, MS220, YEP, YET, YC, YH, YI, YJ, YK, YKE, YKP, YKT, YLT, YLTE, YOL, YOLE, YZL, YZW, OL extension of YF, YG, YP, YTC, YTCE, YL. TOPMAT-EPMN-1002 and TOPMAT-EPMN-3001.

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Table 14 Topiramate Modal Dose and Treatment Duration (CUMULATIVE) Relative to Type of Concomitant AED During Open-Label Adjunctive Treatment of Pediatric Patients

	Any Concomitant AED				NOT EIAED Concomitant AED				EIAED Concomitant AED			
Age Groups	≤ 2*	2 - 9	≤ 9	10-15	≤ 2*	2 - 9	≤ 9	10-15	≤ 2*	2 - 9	≤ 9	10-15
Any Dose												
N	284	453	737	365	104	267	371	152	180	186	366	213
≥ 6 months	204	319	523	278	75	174	249	119	129	145	274	159
≥ 12 months	127	171	298	176	47	89	136	73	49	82	131	103
TPM Modal Dose < 15 mg/kg/day												
N	78	395	473	322	23	235	258	138	55	160	215	184
≥ 6 months	47	266	313	240	15	146	161	105	32	120	152	135
≥ 12 months	25	128	153	143	10	67	77	61	15	61	76	82
TPM Modal Dose ≥ 15 mg/kg/day												
N	206	58	264	43	81	32	113	14	125	26	151	29
≥ 6 months	157	53	210	38	60	28	88	14	97	25	122	24
≥ 12 months	102	43	145	33	37	22	59	12	65	21	86	21
Modal Dose 15 - 30 mg/kg/day												
N	126	53	179	40	46	30	76	13	80	23	103	27
≥ 6 months	86	48	134	36	29	26	55	13	57	22	79	23
≥ 12 months	57	38	95	31	18	20	38	11	39	18	57	20
Modal Dose > 30 mg/kg/day												
N	80	5	85	3	35	2	37	1	45	3	48	2
≥ 6 months	71	5	76	2	31	2	33	1	40	3	43	1
≥ 12 months	45	5	50	2	19	2	21	1	26	3	29	1

* Down to 1 month age (i.e., 1-24 months)

Table 15 Topiramate Modal Dose and Treatment Duration (CUMULATIVE) Relative to Certain Type of Concomitant AED and Topiramate Modal Dose During Open-Label Adjunctive Treatment of Epilepsy in Pediatric Patients

	≤ 2 yo*	2 – 9 yo	≤ 9 yo
TPM Modal Dose > 15 mg/kg/day without EIAED **AND** > 30 mg/kg/day with EIAED			
N	126	35	161
≥ 6 months	100	31	131
≥ 12 months	63	25	88
TPM Modal Dose ≥ 15 mg/kg/day without EIAED			
N	81	32	113
≥ 6 months	60	28	88
≥ 12 months	37	22	59
TPM Modal Dose > 30 mg/kg/day with EIAED			
N	45	3	48
≥ 6 months	40	3	43
≥ 12 months	26	3	29

* Down to 1 month age (i.e., 1-24 months)

Figure 1 shows the expected pharmacokinetic curves for pediatric patients 2-10 years old for expected Cmin with certain topiramate dosing (mg/kg/day). For the DNP recommended lower limit target dose of topiramate median Cmin of ~ 8 µg/ml, the targeted mg/kg/day dosing would range from about 13 mg/kg/day for a 2 year old of 12.5 kg weight to about 7 mg/kg/day for a 10 year old of 32.6 kg weight. For the DNP recommended upper limit target dose of topiramate median Cmin of ~ 13 µg/ml, the targeted mg/kg/day dosing would range from about 22 mg/kg/day for a 2 year old of 12.5 kg weight to about 11 mg/kg/day for a 10 year old of 32.6 kg weight. **These curves are also helpful in understanding the projected/imputed median Cmin for certain mg/kg/day dosing (i.e., > 15 mg/kg/day, 15-30 mg/kg/day, and > 30 mg/kg/day) in different pediatric age/weight subgroups of patients treated with topiramate in the long-term, open-label extension adjunctive studies whose safety experience served as an important basis for assessing/determining safety for this NDA.**

Analyses were conducted in the long-term, open-label adjunctive topiramate treatment studies for dose-duration, treatment-emergent adverse events (TEAEs) including SAEs, and TEAEs causing study discontinuation, and serum bicarbonate analyses according to certain topiramate dosing (i.e., < 15 mg/kg/day, ≥ 15 mg/kg/day, 15-30 mg/kg/day, and > 30 mg/kg/day). Vertical lines (Figure 1) are shown to indicate topiramate dosing for 15, 225., and 30 mg/kg/day. These thresholds were shown to indicate the projected topiramate Cmin for the dosing categories ≥ 15 mg/kg/day, 15-30 mg/kg/day, and > 30

Figure 1 Relationships for Steady State Blood Topiramate Trough Concentrations (i.e., median Cmin) and Topiramate Dosing (Mg/Kg/Day) for Different Ages/Weights in Pediatric Patients. The solid lines (blue, purple, green, orange and brown) show the relationship for different body weights (BWT) representing approximate median weights (12.5, 16, 20.5, 25.7 and 32.6 Kg) of 2, 4, 6, 8 and 10 years old pediatrics. The horizontal dashed purple line represents the median C_{MIN} of 8.4 µg/ml in adults and the median C_{MIN} of 13.3 µg/ml in pediatrics (6-9 years) in TOPMAN-EPMN-106.

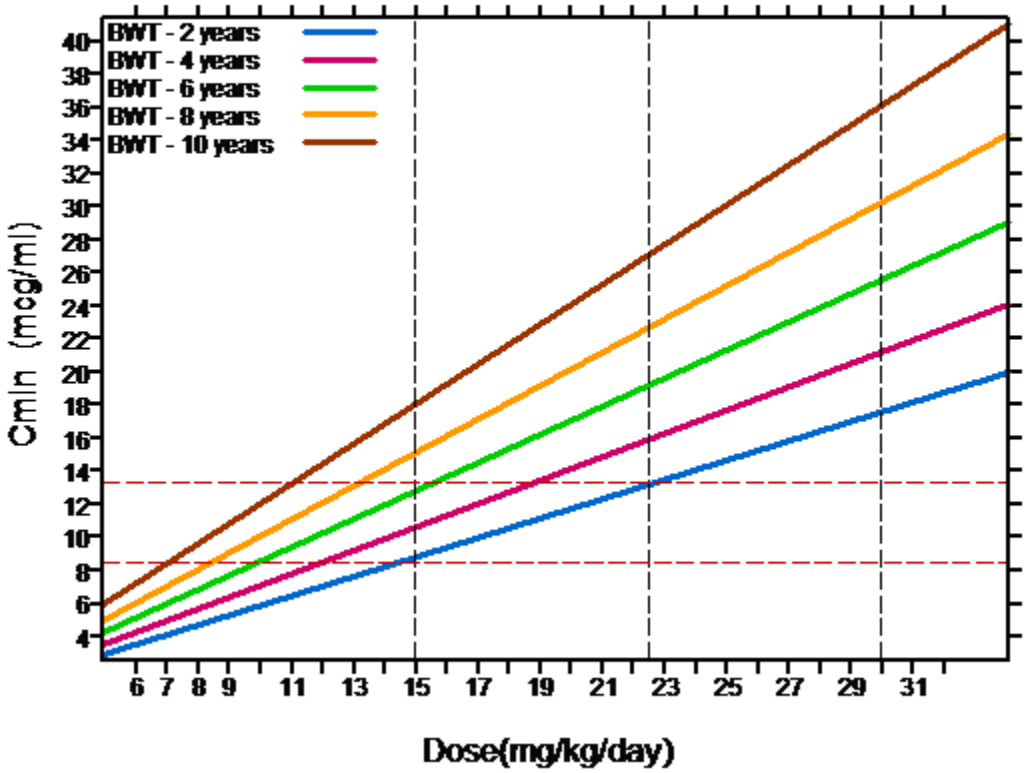

Table 16 Projected Topiramate Blood Steady State Trough (Cmin) Concentrations Relative to Topiramate Dosing (Mg/Kg/Day) for Different Ages/Weights for Pediatric Patients

Age (years)	Weight (Kg) (50 %ile for age)	Topiramate Dosing 15 mg/kg/day	Topiramate Dosing 22.5 mg/kg/day	Topiramate Dosing 30 mg/kg/day
2	12.5	~ 9 µg/ml	~ 13 µg/ml	~ 18 µg/ml
4	16	~ 11 µg/ml	~ 16 µg/ml	~ 21 µg/ml
6	20.5	~ 13 µg/ml	~ 19 µg/ml	~ 26 µg/ml
8	25.7	~ 15 µg/ml	~ 22 µg/ml	~ 30 µg/ml
10	32.6	~ 18 µg/ml	~ 27 µg/ml	~ 37 µg/ml

mg/kg/day. Because I did not have detailed information on the distribution of the dosing in the 15-30 mg/kg/day dosing category, I have shown the middle (i.e., 22.5 mg/kg/day) of this dose range to represent the possible exposures for this dose range. The intersection of each of the vertical lines with each of the different age/weight curves will show various Y-intercepts for Cmin that will suggest the median Cmin that would be expected with the topiramate dosing ranges analyzed. Table 16 shows the range of the various Y-intercepts that suggested the projected/expected median topiramate steady-state Cmin for different weight pediatric patients from 2-10 years old for different topiramate dosing (mg/kg/day). Considering that the upper target for topiramate dosing is ~ 13 µg/ml. Table 16 shows that the PK exposures (13 - 18 µg/ml) in patients aged, 6-10 years treated with at least 15 mg/kg/day would be expected to be similar to or exceed this upper target dose that would achieve a Cmin of about 13 µg/ml. The median Cmin for patients 2-4 years (9-11 µg/ml) and treated with at least 15 mg/kg/day would be slightly below the Cmin upper limit target dose that would achieve a level of about 13 µg/ml. However, considering that the topiramate dosing category is ≥ 15 mg/kg/day, the projected/expected Cmin would in many patients exceed the median value shown in Table 16 because the dosing would be > 15 mg/kg/day but the PK exposure for this dosing category was shown at 15 mg/kg/day. For the 15-30 mg/kg/day dosing category, all projected/expected Cmin topiramate exposures for all ages/weights would exceed 13 µg/ml if one assumes a dosing of 22.5 mg/kg/day to represent the dose range of 15 - 30 mg/kg/day. For the > 30 mg/kg/day dosing, all projected median Cmin exposures (18 – 37 µg/ml) would greatly exceed the 13 µg/ml exposure for the DNP recommended upper limit target dosing and corresponding PK exposure.

Reviewer Comment

- Based upon the relatively high topiramate dosing described for the adjunctive, long-term, open-label treatment, the associated acceptable safety experience with that treatment, and the expected topiramate PK exposures (Table 16) with such dosing, I believe that significant safety assurance can be obtained from this safety experience (i.e., ≥ 15 and > 30 mg/kg/day without concomitant EIAED; and > 30 mg/kg/day with concomitant EIAED) because significant numbers of pediatric patients (≤ 2 years and 2-9 years) would have been exposed to topiramate concentrations presumably exceeding those concentrations expected with DNP recommend dosing of pediatric patients 2-9 years with topiramate monotherapy.

- Initially, the 15 mg/kg/day threshold without a concomitant EIAED was selected as one important daily dosing threshold for the open-label adjunctive safety experiences based upon the infant/toddler study which showed a topiramate (without any concomitant EIAED) mean Cmin of about 13 µg/ml. However, at the time that this dosing threshold was selected, it was not appreciated by this reviewer that topiramate PK clearance in infants/toddlers is decreased relative to that of older pediatric patients (i.e., 2-4 years). Thus, infants/toddlers (e.g., < 2 years old) receiving the same daily dosing (e.g., 15 mg/kg/day) as older pediatric patients (e.g., 2-4 years) would be expected to have higher PK exposures of topiramate (because of decrease topiramate clearance in infants/toddlers) than that of these older pediatric patients. Along this line of thinking, one would expect that young pediatric patients (e.g., 2-4 years) would have lower topiramate exposures than infants/toddlers (e.g., < 2 years) given the same dosing, such as 15 mg/kg/day. Indeed, Table 16 supports this thinking because it shows that young pediatric patients 2-4 years would be expected to have Cmin topiramate exposures ranging from ~ 9-11 µg/ml, levels lower than that shown in the infant/toddler PK study with topiramate 15 mg/kg/day.

Of additional relevance, it is also important to recall that topiramate clearance in young pediatric patients (e.g., 2-5 years) is greater than that for older pediatric patients (e.g., 6-9 years) and that such clearance decreases with pediatric age/weight (although actually the important variable is weight when clearance is compared on a weight/ kg per kg basis). Thus, on a weight adjusted basis, topiramate clearance (starting at ~ 2 years old) is inversely related to pediatric ages. Important corollaries to these observations/facts are that : 1) topiramate clearance in pediatric patients is not only greater than that of adults but that topiramate clearance is also greater in young pediatric patients than in older pediatric patients; and 2) when pediatric patients are all treated with the same mg/kg/day dosing, lower topiramate levels/exposures are observed in the younger pediatric patients and higher levels/exposures are observed in older pediatric patients. Consequently, when pediatric patients 2-9 years old in my analyses were treated with $\geq$ 15 mg/kg/day topiramate, and significant PK exposures were projected in the 2-5 year old group, PK exposures would be expected to be even greater in the 6-9 year old patients.

- **In summary, these supplementary analyses further reinforce the conclusion of the safety of monotherapy for patients 2-9 years by indicating that the acceptable safety experience observed with treatment of young pediatric patients ($\leq$ 9 years) with relatively high topiramate dosing (on mg/kg/day basis during long-term, open label, adjunctive therapy extension studies) was likely associated with topiramate levels/PK exposures that are not only similar to levels/PK exposures expected with DNP recommended dosing of monotherapy in patients 2-9 years but often greatly exceeding these levels/PK exposures.**

Table 17 Statistics for Average and Maximal Daily Topiramate Dose (mg/kg/day) for Adjunctive and Monotherapy Treatment of Partial Epilepsy of Adults and Pediatric Patients in Randomized, Double-blind, Controlled Studies (Placebo-controlled in Adjunctive Treatment and Low dose-controlled in Monotherapy) and Open-Label Pooled Extension Studies

Age Group	Dose Perspective	Adjunctive Treatment of Partial Epilepsy (Pooled Studies)												Monotherapy of Partial Epilepsy											
		Randomized, double-blind, placebo-controlled studies Topiramate dose (mg/kg/day) (Target dose 6 mg/kg/day) *						Open-Label Extension Studies Topiramate dose (mg/kg/day)						Randomized, DoubleBlind, Monotherapy Study 106 (Target dose 400 mg/day)						Open-Label Extension Studies (Pooled Studies)					
		N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max
2-5 years old	Mean Average Daily dose	**21**	**4.9**	0.9	**4.8**	3.3	6.5	**198**	**7.1**	4.6	**6.1**	0.6	25.8	**0**						**0**					
	Mean Maximal Daily dose		**6.4**	1.1	**6.0**	5.2	9.5		**10.5**	7.8	**8.0**	0.9	46.6												
6-9 years old	Mean Average Daily dose	**29**	**5.2**	1.7	**5.0**	1.8	11.3	**255**	**7.2**	4.6	**6.2**	0.9	25.0	**20**	**10.1**	4.2	**10.7**	1.0	15.0	**41**	**8.5**	4.0	**8.2**	1.7	15.3
	Mean Maximal Daily dose		**6.8**	2.7	**6.2**	2.2	16.3		**10.4**	6.7	**8.9**	1.1	40.1		**12.4**	4.3	**13.4**	1.4	16.7		**11.2**	5.2	**11.8**	2.5	27.6
10-15 years old	Mean Average Daily dose	47	**4.6**	1.3	4.9	1.1	6.8	365	**7.0**	4.7	5.8	0.4	33.6	57	**7.5**	2.8	7.6	0.9	13.1	**112**	7.5	3.5	7.4	1.7	25.8
	Mean Maximal Daily dose		**6.1**	1.7	6.1	1.8	10.4		**10.2**	7.4	7.9	0.4	43.3		**8.9**	2.9	9.1	1.8	15.4		9.2	4.5	8.5	2.0	32.3
≥ 16 years old	Mean Average Daily dose	74	**3.5**	1.4	3.6	0.6	6.0	2891	**7.2**	5.1	6.0	0	46.4	159	**3.7**	2.1	4.0	0.2	9.4	**348**	5.0	2.3	4.9	0	14.6
	Mean Maximal Daily dose		**5.3**	2.1	5.3	0.6	14.3		**10.4**	7.6	8.8	0	67.0		**4.9**	2.4	5.0	0.4	10.5		6.6	3.1	6.3	0	29.6

***Majority of patients on concomitant enzyme-inducing AED s that decrease topiramate levels**
Med = median
Min = minimum
Max = maximum

The following table shows the number of patients that were randomized to various daily doses of topiramate in the three randomized, double-blind, controlled, monotherapy studies (104, 105, 106).

Table 18 **Numbers of Patients (According to Age Group) Randomized to Various Daily Doses of Topiramate in Pivotal Monotherapy Trials (104, 105, 106)**

Randomized Topiramate Dose (mg)	Study ID	6-9 yo	10-15 yo	>=16 yo	Any age
25	104	8	8	4	20
50	104		5	100	105
50	106	17	57	160	234
100	105	7	23	180	210
200	104	7	4	3	14
200	105	8	21	170	199
400	106	20	57	159	236
500	104		3	110	113

The following series of tables (Table 19 - Table 24) exhibit various information/insight into how well the youngest pediatric patients (6-9 years) who were randomized to 400 mg topiramate daily (in pivotal Study 106) were able to tolerate and take topiramate (including for specific durations) compared to older pediatric patients (10-15 years) and to adults (≥ 16 years). Data shown in these tables were derived from special analyses that I requested from the sponsor. Results for patients 6-9 years are highlighted in yellow and bolded for emphasis.

Table 19 **Percentage (%) of Patients with Modal TPM Daily Dose in Monotherapy Study 106**

Treatment Period (Days)	TPM 50 mg Dose Group (6-9yo, N=17; 10-15yo, N=57; ≥ 16yo,N=160)						400 mgTPM Dose Group (6-9yo, N=20; 10-15yo, N=57; ≥ 16yo,N=159)					
	25 mg/day			50 mg/day			300-399 mg/day			400 mg/day		
	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0
= 60	6	0	6	**82**	86	69	**5**	2	6	**75**	84	58
61-120	6	0	4	**76**	81	56	**10**	5	10	**65**	81	48
121-240	6	0	3	**53**	67	45	**10**	7	9	**40**	68	33
241-300	6	0	3	**53**	56	38	**10**	11	10	**35**	58	26
301-364	6	0	1	**35**	44	28	**10**	5	8	**30**	49	19
> = 365	12	0	1	**29**	42	28	**10**	5	9	**30**	47	19

Table 20 Percentage (%) of Patients with Full* Randomized TPM Dose for Full Treatment Duration in Monotherapy Study 106

Treatment Period (Days)	TPM Dose Group					
	50 mg/day (6-9yo, N=17; 10-15yo, N=57; ≥ 16yo,N=160)			400 mg/day (6-9yo, N=20; 10-15yo, N=57; ≥ 16yo,N=159)		
	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0
= 60	**71**	65	54	**75**	81	50
61-120	**71**	75	54	**65**	74	47
121-240	**47**	67	39	**40**	63	29
241-300	**53**	56	37	**35**	58	25
301-364	**29**	42	27	**30**	47	19
> = 365	**29**	40	24	**30**	42	16

* "Full" randomized dose = ≥ 90 % of randomized dose

Table 21 Percentage (%) of Patients with Maximal TPM Daily Dose in Monotherapy Study 106

Treatment Period (Days)	(6-9yo, N=20; 10-15yo, N=57; ≥ 16yo,N=159) 400 mg TPM Dose Group											
	< or = 199 mg/day			200- 299 mg/day			300-399 mg/day			400 mg/day		
	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0	6-9 yo	10-15yo	≥ 16 y0
= 60	5	4	22	0	4	6		2		**90**	91	67
61-120	0	2		0	0	3	**0**	2	5	**80**	86	59
121-240	0	2	5	0	0	2	**5**	5	6	**65**	81	48
241-300	0	0	3	0	0	0	**10**	9	10	**40**	67	30
301-364	0	2	3	0	0	1	**10**	9	12	**35**	58	26
> = 365	0	0	2	0	2	1	**10**	4	10	**30**	49	19
			1						9			

Table 22 Percentage (%) of Patients with Modal TPM Daily Dose (mg/kg/day) for 400 mg Dose Group (6-9yo, N=20; 10-15yo, N=57; ≥ 16yo,N=159)

Treatment Period (Days)	< 4.5 mg/kg/day			4.5- <7 mg/kg/day			7- <9 mg/kg/day			9- <11 mg/kg/day			11- <13.5mg/kg/day			13.5-<15 mg/kg/day			≥ 15mg/kg/day		
	6-9 yo	10 - 15yo	≥16 yo	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10- 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 yo	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 y0
= 60	5	11	26	0	18	35	**5**	19	11	**20**	23	2	**20**	18	0	**10**	2	0	**25**	0	0
61-120	0	5	19	0	14	35	**5**	28	9	**10**	19	1	**25**	19	0	**10**	2	0	**25**	0	0
121-240	0	4	12	0	11	25	**5**	26	7	**0**	14	1	**10**	21	0	**20**	0	0	**15**	0	0
241-300	0	4	11	0	14	19	**5**	21	8	**0**	14	1	**10**	12	0	**20**	4	0	**10**	0	0
301-364	0	4	8	0	12	15	**5**	18	6	**0**	14	1	**5**	4	0	**20**	4	0	**10**	0	0
> = 365	0	7	9	0	11	14	**5**	19	6	**5**	9	1	**5**	7	0	**15**	2	0	**10**	0	0

Table 23 Percentage (%) of Patients with Full* Randomized TPM Daily Dose (mg/kg/day) For Full Treatment Duration for 400 mg Dose Group (6-9yo, N=20; 10-15yo, N=57; ≥ 16yo,N=159)

Treatment Period (Days)	< 4.5 mg/kg/day			4.5- <7 mg/kg/day			7- <9 mg/kg/day			9- <11 mg/kg/day			11- <13.5mg/kg/day			13.5-<15 mg/kg/day			≥ 15mg/kg/day		
	6-9 yo	10 - 15yo	≥16 yo	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10- 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 yo	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 y0
= 60	0	2	10	0	21	33	**5**	25	6	**15**	14	2	**20**	18	0	**5**	2	0	**30**	0	0
61-120	0	2	9	0	16	30	**5**	19	6	**10**	18	1	**15**	18	0	**5**	2	0	**30**	0	0
121-240	0	2	6	0	18	19	**0**	16	4	**0**	12	1	**10**	16	0	**5**	0	0	**25**	0	0
241-300	0	2	6	0	16	16	**0**	14	3	**0**	12	1	**10**	14	0	**5**	0	0	**20**	0	0
301-364	0	2	3	0	16	13	**0**	12	3	**0**	7	1	**10**	11	0	**0**	0	0	**20**	0	0
> = 365	0	0	3	0	14	10	**0**	11	3	**0**	7	1	**10**	11	0	**0**	0	0	**20**	0	0

***** "Full" randomized dose = ≥ 90 % of randomized dose

Table 24 Percentage (%) of Maximal TPM Daily Dose for 400 mg Dose Group (6-9yo, N=20; 10-15yo, N=57; ≥ 16yo,N=159)

Treatment Period (Days)	< 4.5 mg/kg/day			4.5- <7 mg/kg/day			7- <9 mg/kg/day			9- <11 mg/kg/day			11- <13.5mg/kg/day			13.5-<15 mg/kg/day			≥ 15mg/kg/day		
	6-9 yo	10 - 15yo	≥16 yo	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10- 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 yo	6-9 yo	10 - 15yo	≥16 y0	6-9 yo	10 - 15yo	≥16 y0
= 60	10	11	41	0	18	45	**5**	26	12	**15**	23	2	**30**	21	0	**10**	2	0	**30**	0	0
61-120	0	5	20	0	14	36	**5**	25	14	**15**	25	2	**30**	19	0	**10**	2	0	**25**	0	0
121-240	0	5	18	0	11	31	**5**	28	13	**10**	21	1	**20**	18	0	**15**	4	0	**25**	2	0
241-300	0	4	12	0	12	23	**5**	26	8	**0**	18	1	**10**	12	0	**20**	4	0	**15**	0	0
301-364	0	6	11	0	12	18	**5**	19	8	**0**	16	1	**10**	12	0	**20**	4	0	**10**	0	0
> = 365	0	2	9	0	14	14	**5**	19	6	**0**	11	1	**5**	5	0	**20**	4	0	**10**	0	0

Reviewer Comment

- Table 19 shows the percentage of patients with a modal dose relative to the randomized dose or a lower dose in various age subgroups in the pivotal study (Study 106), that demonstrated efficacy, for various durations up to 1 year. Tolerability was shown if the dose was used for any time during a specific treatment period. Of interest, 75 % of patients 6-9 years tolerated the 400 mg randomized dose for the first two months, which involved a 6 week titration up to this dose. This percentage was mildly lower than that for older pediatric patients 10-15 years but was notably greater than the percentage for adults. With continuing treatment up to one year, the percentage of patients 6-9 years tolerating a 400 mg modal daily topiramate dose gradually decreased over time during the first 8 months, but the percentage was relatively stable between 8-12 months of treatment remained at 30 - 35 %. At the end of one year of treatment, tolerability of a 400 mg modal dose in patients 6-9 years (30 %) was less than that of older pediatric patients 10-15 years (47 %), but it was greater than the percentage for adults (19 %).

  Table 19 which did not require treatment throughout the full specific duration. At the end of one year, the percentage of patients tolerating the "full" 400 mg dose was 30 % in patients 6-9 years, was 42 % in patients 10-15 years, but was only 16 % in adults.

- Table 20 shows the percentage of patients in various age subgroups who tolerated the full 400 mg or 50 mg randomized, daily, topiramate dose for the full, specific, treatment durations. For the 400 mg dose, the percentage who tolerated the full dose up to 2 months was 75 % for 6-9 year old patients, 81 % for 10-15 year old patients, and only 50 % for adults (≥ 16 years). Thus, tolerability was similar in both pediatric age subgroups, and tolerability in all pediatric patients was notably better than that for adults. The percentages for each age subgroup and for each duration **(requiring treatment throughout each whole specific treatment duration)** in Table 20were quite similar to those percentages in Table 19 for the modal dose data analyses.

- Table 21 shows the percentage of patients achieving a specific maximal dose/dose ranges for various, specific treatment durations in various age subgroups for patients randomized to the 400 mg daily topiramate dose in Study 10. Tolerability was shown if the dose was used for any time during a specific treatment period. Most (90 %) of the 6-9 year old patients achieved a maximal, randomized dose of 400 mg within the first 2 months of treatment and this percentage gradually decreased over an ensuing year of treatment. At the end of one year, 30 % in the youngest pediatric age subgroup were taking the 400 mg dose and 10 % were taking a maximal dose ranging from 300-399 mg. Thus, at the end of one year, 40 % of patients in this age group were taking a maximal dose ranging between 300-400 mg daily. Compared to the maximal doses achieved in various epoch duration over 1 year, the percentage of tolerability in the youngest pediatric age subgroup was mildly less than that of older pediatric patients 10-15 years, but it was better than that for adults.

- Table 22 shows the percentage of patients with a modal dose (mg/kg/day) relative to the randomized 400 mg dose in various age subgroups in Study 106 for various durations up to 1 year. Tolerability was shown if the dose was used for any time during a specific treatment period. Whereas 25 % of 6-9 year old patients had a modal dose of ≥ 15 mg/kg/day for the first two months of treatment, the modal dose in 55 % of this same age subgroup was ≥ 11 mg/kg/day. Up to the end of one year of treatment, 10 % of these patients was taking a modal dose of ≥ 15 mg/kg/day, and 30 % was taking a modal dose of ≥ 11 mg/kg/day. For older patients, the first dose range in which there was a notable percentage of patients was 11- < 13.5 mg/kg/day for older pediatric patients 10-15 years and was 7 - < 9 mg/kg/day for adults (≥ 16 years). The modal dose range containing the greatest percentage of

patients over one year of treatment was ≥ 15 mg/kg/day for 6-9 year old patients, 7 - < 9 mg/kg/day for 10-15 year old patients, and 4.5 - < 7 mg/kg/day for adults.

- Table 23 shows the percentage of patients in various age subgroups who tolerated the full 400 mg daily, topiramate dose (as mg/kg/day dosing) for the full, specific, treatment durations. The **highest dose range** for which the largest percentage of patients received full dosing for each full treatment duration (based upon ≥ 10 % in a dose range) was ≥ 15 mg/kg/day for 6-9 year old patients, 11- < 13.5 mg/kg/day for 10-15 year old patients, and 4.5 - < 7 mg/kg/day for adults. The **dose range containing the largest percentages of patients throughout one year of treatment** was ≥ 15 mg/kg/day for 6-9 year old patients, 7 - < 9 mg/kg/day for 10-15 year old patients, and 4.5 - < 7 mg/kg/day for adults.

- Table 24 shows the percentage of patients achieving a specific maximal dose range (based upon mg/kg/day dosing) for various, specific treatment durations in various age subgroups for patients randomized to the 400 mg daily topiramate dose in Study 106. Tolerability was shown if the dose was used for any time during a specific treatment period. The **highest dose range** in which maximal dosing was received in a significant percentage of patients (based upon ≥ 10 % in a dose range) was ≥ 15 mg/kg/day for 6-9 year old patients, 11- < 13.5 mg/kg/day for 10-15 year old patients, and 7 - < 9 mg/kg/day for adults. The **dose range containing maximal dosing for the largest percentages of patients throughout one year of treatment** was ≥ 15 mg/kg/day for 6-9 year old patients, 7 - < 9 mg/kg/day for 10-15 year old patients, and 4.5 - < 7 mg/kg/day for adults.

- Overall, tolerability of a randomized dose of 400 mg in 6-9 year old patients was relatively good in absolute terms and in some instances better than for adults. In addition, it should be recognized that patients not continuing on for longer treatment durations may not have been included because in inadequate seizure control causing study discontinuation or possibly some other reason unrelated to tolerability or adverse reaction from topiramate. This reasonable tolerability for extended treatment durations is also demonstrated in the mg/kg/day analyses in which significant percentages of these young pediatric patients tolerated dosing at ≥ 15 mg/kg/day. Furthermore, considering that our lower limit target dose is 250 mg for such patients and the upper limit is 350 mg (a higher limit to which a patient could be titrated if necessary because of inadequate seizure control at the lower limit target) for such patients, I expect patients to exhibit reasonable tolerability of our recommended dosing.

7.2.3 Explorations for Dose Response

Explorations of dose-response were for double-blind and open-label study analyses were conducted and discussed in section 7.4.1 (Common Adverse Events) and in section 7.4.2 (Laboratory Findings).

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Not applicable

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable

7.3 Major Safety Results

7.3.1 Deaths

Epilepsy Monotherapy Studies

Among the 1,127 subjects who received topiramate in the epilepsy monotherapy studies, there were 8 deaths. **No deaths occurred in subjects aged 2 to 9 years at study entry.** One death occurred in a 12-year-old subject, Subject 643004 from Study TOPMAT-EPMN-106, who died 2 days after discontinuing from the open-label extension phase of the study following an accident in which he suffered head trauma (Table 25).

The remaining 7 deaths were adult subjects from the open-label extension of Study TOPMAT-EPMN-104. Cause of death in these subjects were as follows: intermittent claudication (peripheral vascular disease), pulmonary carcinoma, cerebrovascular disorder and intestinal obstruction, arrhythmia, aspiration, sepsis, and seizures. All deaths were considered by the investigator to be of unlikely relationship to topiramate.

Table 25 Listing of Pediatric Deaths in the Epilepsy Monotherapy Studies (Epilepsy Monotherapy)

Study ID/ Subject ID Death Date	Age (Yrs)/ Sex/ Race	AE Onset Phase Treatment Group	Onset Date, Day of AE Onset[a] Dose[b]	Body System Preferred Term Reported Term	Serious AE?	Stop Date, Duration (days)	Severity, Relationship	Action Taken
Country Identifier: Argentina Investigator Name: Lafuente, Alicia								
Topmat-epmn-106	12	Open-label	11Mar2003	Liver and biliary system disorders	No	21Mar2003	Mild	None
643004	M	TPM	678	Hepatic function abnormal		11	Doubtful	
[redacted]	W		400	High transaminases				
			11Mar2003	White cell and RES disorders	No	21Mar2003	Mild	None
			678	Eosinophilia		11	Not related	
			400	Eosinophilia				
			11Mar2003	White cell and RES disorders	No	21Mar2003	Mild	None
			678	Lymphocytosis		11	Not related	
			400	Lymphocytosis				
			[redacted]	Body as a whole - general disorders	Yes	[redacted]	Marked	Drug stopped permanently
			686	Injury		3	Doubtful	
				Head trauma				

[a] Study day relative to first day of study medication (day 1).
[b] Dose unit is mg/day.
Sex: F=Female, M=Male, Race: A=Asian, B=Black or African American, O=Other, W=White.
For each subject who died, adverse events are listed where the recorded adverse event stop date is the same as the death date or the stop date is missing.
tae_dth_mn.rtf generated by death_mono.sas.

Epilepsy Adjunctive Therapy Studies

Of the 4,067 subjects who received topiramate in epilepsy adjunctive therapy studies, 37 subjects died.

Three deaths occurred in subjects aged 2-9. Subject 49 entered Study YL, which was conducted in Lennox-Gastaut syndrome patients, at age 8 with severe developmental delays; his concomitant AEDs included clonazepam and valproic acid. He received topiramate for approximately 1.5 years. His death from cardiac arrest was considered by the investigator to be doubtfully related to topiramate. The other 2 deaths in the 2-9 age group occurred in Study EPPD-002 (Subjects 58 and 838), an uncontrolled study that enrolled pediatric subjects aged 1 to 18 years with inadequately controlled POS, GTC, seizures associated with Lennox-Gastaut syndrome, and myoclonic or absence seizures.

Both subjects were receiving at least 2 concomitant AEDs; one subject was mentally retarded and the other had cerebral palsy and a significant medical history of gastroesophageal reflux and recurrent pneumonia. Both of these deaths, which were considered unrelated to study drug by the investigator, were associated with pneumonia, a common cause of death in epilepsy patients.

Three deaths occurred in subjects aged 10-15. Subject 529 from Study YP experienced sudden death at age 16 after more than 2 years of topiramate treatment. The subject's death from unknown reasons was considered to be possibly related to the study drug by the investigator. The remaining 2 deaths, which occurred in Study EPPD-002 (Subjects 302 and 854), were associated with pneumonia and/or sudden death and were considered doubtfully related to study drug by the investigator.

Of the 31 adult subjects whose deaths were reported in the adjunctive therapy studies, most experienced unexplained or sudden death or died of seizure-related causes (e.g., aspiration, accidents).

Brief descriptions of the 6 pediatric subjects who died during the epilepsy adjunctive therapy studies are outlined in Table 26. Full narratives were also provided for patients who died.

Table 26 Listing of Pediatric Deaths in the Epilepsy Adjunctive Therapy Studies (Epilepsy Adjunctive Therapy)

Study Id/ Subject Number/ Death Date	Age (Yrs)/ Sex/ Race	Analysis Phase Treatment Group	Onset Date, Day of AE Onset [a] Dose [b]	Body System Preferred Term Reported Term	Serious AE?	Stop Date, Duration (days)	Severity, Relationship	Action Taken
Country: Brazil Investigator Full Name: Manreza, Maria Luiza								
EPPD-002	6	Open-label	15Oct1999	Psychiatric disorders	No		Mild	None
838	M	TPM	1	Anorexia			Possible	
[redacted]	B		25.0	Anorexia				
			15Oct1999	Psychiatric disorders	No		Mild	None
			1	Somnolence			Possible	
			25.0	Somnolence				
			17Mar2000	Centr & periph nerv syst disorders	No		Mild	None
			155	Ataxia			Probable	
			300	Ataxia				
			01Aug2000	Respiratory system disorders	No	05Aug2000	Marked	Drug stopped
			292	Pneumonia		5	Not related	permanently
			350	Pneumonia				
			[redacted]	Respiratory system disorders	Yes	[redacted]	Marked	Drug stopped
			294	Pleural effusion		3	Not related	permanently
			350	Left pleural effusion				
			[redacted]	Respiratory system disorders	Yes	[redacted]	Marked	Drug stopped
			294	Pneumonia		3	Not related	permanently
			350	Bilateral pneumonia				
Country: Brazil Investigator Full Name: Marilisa								
EPPD-002	15	Open-label	24Sep1999	Psychiatric disorders	No		Mild	None
854	F	TPM	22	Somnolence			Probable	
[redacted]	W		100	Somnolence				
Country: Brazil Investigator Full Name: Marilisa (continued)								
EPPD-002	15	Open-label	15Oct1999	Respiratory system disorders	No	25Nov1999	Mild	None
854	F	TPM	43	Sputum increased		42	Doubtful	
[redacted]	W		100	Bronchial hypersecretion				
			20Nov1999	Respiratory system disorders	Yes	25Nov1999	Marked	None
			79	Pneumonia		6	Doubtful	
			100	Pneumonia				
			[redacted]	Respiratory system disorders	Yes	[redacted]	Marked	None
			79	Respiratory insufficiency		6	Doubtful	
			100	Respiratory insufficiency that caused death				
Country: Canada Investigator Full Name: Buckley								
EPPD-002	8	Open-label	(b) (6)	Respiratory system disorders	Yes	[redacted]	Marked	Drug stopped
58	F	TPM	21	Aspiration		1	Not related	permanently
[redacted]	W		75.0	Aspiration				
			(b) (6)	Respiratory system disorders	Yes	[redacted]	Marked	None
			21	Respiratory depression		1	Not related	
			75.0	Respiratory arrest				
Country: Canada Investigator Full Name: Cooper								
EPPD-002	11	Open-label	(b) (6)	Centr & periph nerv syst disorders	Yes	[redacted]	Marked	Drug stopped
302	F	TPM	23	Encephalopathy		1	Doubtful	permanently
(b) (6)	W			Mild focal lymphocytic encephalitis				
			(b) (6)	Resistance mechanism disorders	Yes	[redacted]	Marked	Drug stopped
			23	Sepsis		1	Doubtful	permanently
				Sepsis				

(Continued)

Table 24: (Continued) Listing of Pediatric Deaths in the Epilepsy Adjunctive Therapy Studies (Epilepsy Adjunctive Therapy)

Study Id/ Subject Number/ Death Date	Age (Yrs)/ Sex/ Race	Analysis Phase Treatment Group	Onset Date, Day of AE Onset [a] Dose [b]	Body System Preferred Term Reported Term	Serious AE?	Stop Date, Duration (days)	Severity, Relationship	Action Taken
Country: Canada Investigator Full Name: Cooper (continued)								
EPPD-002	11	Open-label	03Apr1999	Respiratory system disorders	Yes	03Apr1999	Marked	Drug stopped
302	F	TPM	23	Pneumonia		1	Doubtful	permanently
[redacted]	W			Localized pneumonia				
Country: USA Investigator Full Name: Elterman, Roy								
YP	13	Double-blind	10Nov1995	Respiratory system disorders	No		Mild	None
529	F	TPM 6 mg/kg/day	39	Upper resp tract infection			Doubtful	
[redacted]	W		300	Cold-cough & sinus congestion				
			23Dec1995	Centr & periph nerv syst disorders	No	14Jun1998	Mild	None
			82	Speech disorders/related speech problems		905	Possible	
			400	Perservation				
			23Dec1995	Psychiatric disorders	No		Mild	None
			82	Neurosis			Possible	
			400	Compulsive behavior				
		Open-label	14Mar1996	Centr & periph nerv syst disorders	No		Mild	Dose reduced
		TPM	164	Paraesthesia			Possible	
			400	Tingling in feet and legs				
		Open-label	30Apr1996	Skin and appendages disorders	No	14Jun1998	Mild	None
		TPM	211	Livedo reticularis		776	Possible	
			350	Livedo reticularis				
			01Jan1998	Skin and appendages disorders	No	14Jun1998	Mild	None
			822	Hypertrichosis		165	Possible	
			375	Increased hair growth				
			[redacted]	Body as a whole - general disorders	Yes	[redacted]	Marked	Drug stopped
			986	Sudden death		1	Possible	permanently
				Death of unknown origin				
Country: USA Investigator Full Name: Levisohn, Paul								
YL	8	Double-blind	22Jul1995	Psychiatric disorders	No		Moderate	Drug stopped
49	M	TPM 6 mg/kg/day	7	Somnolence			Possible	temporarily
[redacted]	W		25.0	Lethargy				
			17Aug1995	Platelet,bleeding & clotting disorders	No		Mild	None
			33	Purpura			Doubtful	
			50.0	Bruises arms				
			17Aug1995	Skin and appendages disorders	No		Mild	None
			33	Skin disorder			Doubtful	
			50.0	Abdominal scar				
		Open-label	16Jan1996	Platelet,bleeding & clotting disorders	No		Mild	Other
		TPM	185	Thrombocytopenia			Doubtful	
			150	Thrombocytopenia				
			[redacted]	Heart rate and rhythm disorders	Yes	[redacted]	Marked	Drug stopped
			552	Cardiac arrest		1	Doubtful	permanently
				Cardiorespiratory arrest				

[a] Study day relative to first day of study medication (day 1).
[b] Dose unit is mg/day.
[c] The investigator recorded the date of death as occurring 1 day before the AE that lead to death.
Sex: F=Female, M=Male, Race: A=Asian, B=Black or African American, O=Other, W=White.
For each subject who died, adverse events are listed where the recorded adverse event stop date is the same as the death date or the stop date is missing.
tae_dth_adj.rtf generated by death_adj.sas.

Non-epilepsy Indication Studies

There were no deaths in these studies.

Reviewer Comment

- There was no suggestion of a problem with regard to an increased risk for deaths associated with topiramate treatment in young pediatric patients (2-9 years).

7.3.2 Nonfatal Serious Adverse Events

Epilepsy Monotherapy

In the double-blind phase of the key monotherapy Study 106, there was only 1 patient with a serious adverse event (SAE), male testis disorder, in the randomized 50 mg topiramate daily dose group (N=17; 6 %) for patients 6-9 years. There were no SAEs in the randomized 400 mg topiramate daily dose group (N=20; 0 %) in patients 6-9 years In contrast, the incidence of SAEs was 8 % in adults (N=159) and 2 % in patients 10-15 years in the 400 mg dose group. The incidence of SAEs was 6 % in adults and 9 % in patients 10-15 years in the 50 mg dose group.

The SAE experience with very limited numbers of patients 6-9 years in the other monotherapy studies was not relevant.

Adjunctive Treatment of Epilepsy

In the pooled double-blinded, placebo-controlled, adjunctive studies, four (8 %) 2-9 year old patients (out of 50) treated with topiramate (target dose 6 mg/kg/day) experienced 5 SAEs (i.e., convulsion aggravated, urinary tract infection, gastroesophageal reflux, pneumonia, and coagulation time increased). Three (6 %) 2-9 year old patients (out of 53) treated with placebo experienced 3 SAEs (i.e., convulsions aggravated, infection viral).

In Study YP (the randomized, double-blind, placebo-controlled study that was the basis of FDA approval of topiramate for adjunctive treatment of partial epilepsy in pediatric patients 2- 16 years), there were no SAEs in 22 patients treated with topiramate (target dose 6 mg/kg/day). Three of the 22 patients treated with placebo experienced 3 SAEs (i.e., convulsions aggravated, infection viral).

Non-Epilepsy Treatment Indications

The SAE experience in the non-epilepsy treatment studies for patients 6-9 years was not relevant. Relatively small numbers of patients were studied and the dose range (usually < 3 mg/kg/day) was very low compared to the planned topiramate dosing (6-22 mg/kg/day) in monotherapy in young patients 2-9 years.

Reviewer Comment

- There was no clear signal of serious adverse event/reaction toxicity associated with topiramate treatment in the young pediatric patients 2-9 years compared to older patients (older pediatric patients or adults).

7.3.3 Dropouts and/or Discontinuations

Epilepsy Monotherapy

In Study 106 (pivotal DB Monotherapy Epilepsy study demonstrating efficacy and safety of topiramate for patients 10 years and older), the incidence of patients who discontinued due to an adverse events was 20 % (4/20) for the 400 mg dose in patients 6-9 years. This incidence was only mildly higher than that in patients 10-15 years (12 %), and was similar to that observed in adults (22 %). In the 6-9 year group, four patient discontinuations there were various adverse events including fever (2), flushing (2), confusion (1), aggressive reaction (1) and malaise, . The incidence of discontinuations in the 50 mg randomized dose groups was higher for 6-9 years (18 %; 3/18) than that in the 10-15 year group (2 %; 2/57) and in the adult group (11 %; 17/160). In the 6-9 year group, there were 4 adverse events (insomnia, somnolence, fatigue, rash) associated with the 3 patient discontinuations.

The experience with TEAEs causing study discontinuation with very limited numbers of patients 6-9 years in the other, controlled monotherapy studies was not relevant.

Adjunctive Treatment of Epilepsy

In the pooled, double-blind adjunctive studies, no 2-9 year old patients (out of 50) treated with topiramate (target dose 6 ,g/kg/day) discontinued from a study because of a TEAE.

Non-Epilepsy Treatment Indications

The experience with TEAEs causing study discontinuation in the non-epilepsy treatment studies for patients 6-9 years was not relevant. Relatively small numbers of patients were studied and the topiramate dose range (usually < 3 mg/kg/day) was very low compared to the planned topiramate dosing (6-22 mg/kg/day) in monotherapy in young patients 2-9 years.

Reviewer Comment

- There was no clear signal of adverse event/reaction toxicity associated with topiramate treatment causing study discontinuations in the young pediatric patients 2-9 years compared to older patients (older pediatric patients or adults).

7.3.4 Significant Adverse Events

Table 27 shows a list of Designated Medical Events (DMEs) that are considered medically serious adverse event reactions in CDER and CBER at the Agency.

Table 28 shows a list of MedDRA preferred terms for the DMEs in Table 27.

Table 27 List of CDER/CBER Designated Medical Events (DME) Reactions

Acute pancreatitis

Acute respiratory failure
Agranulocytosis
ALS
Anaphylaxis and anaphylactoid reactions
Aplastic anemia
Blind

Colitis ischemic
Congenital anomalies
Deaf

Diss. intravascular coagulation
Endotoxic shock, confirmed or suspected
Hemolysis

Hemolytic anemia

Liver failure
Liver necrosis
Liver transplant
Neuroleptic malignant syndrome
Pancytopenia
PML
Product infectious disease transmission

Pulmonary fibrosis
Pulmonary hypertension
Renal failure
Rhabdomyolyisis
Seizure
Serotonin syndrome
Stevens-Johnson syndrome
Sudden death
Suicide
Torsade de Pointes
Toxic epidemal necrolysis
TTP
Ventricular fibrillation

Table 28 List of Preferred Terms (MedDRA 12.1 last updated Oct_2009) for Adverse Events Reflecting DMEs

Pancreatitis, Pancreatitis acute, Pancreatitis hemorrhagic, Pancreatitis necrotizing, Pancreatic necrosis
Acute respiratory failure, Respiratory failure, Acute respiratory distress syndrome
Agranulocytosis, Neutropenia, Febrile neutropenia
Amyotrophic lateral sclerosis
Anaphylactic reaction, Anaphylactoid reaction, Anaphylactic shock, Anaphylactoid shock
Aplastic anemia, Bone marrow failure, Aplasia pure red cell
Blindness, Blindness transient, Blindness unilateral, Optic ischemic neuropathy, Sudden visual loss
Colitis ischemic, Intestinal infarction
Congenital anomaly
Deafness, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness bilateral, Deafness unilateral, Sudden hearing loss
Disseminated intravascular coagulation
Endotoxic shock, Septic shock
Hemolysis, Intravascular hemolysis, Hemoglobinaemia, Hemoglobinuria, Haptoglobin decreased
Hemolytic anemia, Coombs positive hemolytic anemia, Coombs negative hemolytic anemia
Hepatic failure, Hepatic encephalopathy, Acute hepatic failure, Subacute hepatic failure
Hepatic necrosis, Hepatitis fulminant, Hepatitis acute
Liver transplant
Neuroleptic malignant syndrome
Pancytopenia
Progressive multifocal leukoencephalopathy
Transmission of an infectious agent via a medicinal product, Transfusion-transmitted infectious disease, Product contamination microbial
Pulmonary fibrosis
Pulmonary hypertension, Cor pulmonale
Renal failure acute, Renal failure, Renal impairment
Rhabdomyolysis
Convulsion, Epilepsy, Grand mal convulsion
Serotonin syndrome
Stevens-Johnson syndrome, Erythema multiforme
Sudden death, Sudden cardiac death
Completed suicide
Torsade de pointes
Toxic epidermal necrolysis, Dermatitis exfoliative
Thrombotic thrombocytopenic purpura
Ventricular fibrillation

The monotherapy experience for pediatric patients 6-9 years in the randomized, double-blind, phases of the pivotal studies (104, 105, 106) was reviewed for the occurrence of medically serious DMEs outlined in Table 27 and reflected by the various PTs shown in Table 28.

The following summaries are for "medically serious" SAEs which were numerically more frequent in pediatric patients ≤ 9 years old than that in older pediatric patients (10-15 yo) and in adults (≥ 16 yo) during open-label topiramate treatment in monotherapy or adjunctive studies. The preferred terms (PTs) shown in the above lists from OSE and any other medically significant SAEs in the opinion of this reviewer were the focus.

DB Monotherapy (any topiramate daily dose)

In the pooled, randomized, double-blind, controlled monotherapy studies (1-4, 105, 106), the only medical serious adverse event that was more frequent in 6-9 year old patients (N=67) for any topiramate dose was grand mal convulsion (3 %) . There were no grand mal convulsions in patients ≥ 10 years (10-15 years, N=178; adults, N=886).

In Study 106, only 1 young pediatric patient (6-9 yo) experienced an SAE (i.e., testis disorder) and this patient had been randomized to the 50 mg daily topiramate dose. In this study, the number of young pediatric patients (6-9 yo) was 17 and 20 in the 50 mg and 400 mg topiramate daily dose groups. It is noteworthy that there were no medical serious SAEs in the older patients treated with a relatively high daily dose of topiramate (up to 400 mg).

DB Adjunctive Therapy of Epilepsy (any topiramate daily dose)

There were no medically serious adverse events in the adjunctive studies in which the incidence for the young pediatric patients (2-9 years) was greater than that for older pediatric patients (10-15 years) or adults.

Because double-blind, placebo-controlled treatment in infants/toddlers (1-24 months) was very short and limited (only up to 20 days), it is difficult to draw any conclusions from this controlled treatment phase about the risk of medically serious adverse events with topiramate treatment in these very young patients.

Open-Label Monotherapy (any topiramate daily dose)

In the open-label, extension monotherapy studies, the only medical serious adverse event that was more frequent in 6-9 year old patients (N=41) for any topiramate dose was grand mal convulsion (2.4 %) . The incidence of grand mal convulsions in adults (N=347) was 1.4 %. There were no grand mal convulsions in patients pediatric patients 10-15 years (N=178).

Open-Label Adjunctive Treatment (any topiramate daily dose)

Table 29 shows the incidence of medically serious adverse events in open-label, adjunctive treatment, extension studies in which the frequency of a medically serious adverse event was numerically greater in

a very young pediatric population (1-24 months or 2-9 years) compared to the experience in older pediatric patients (10-15 years) or adults.

Table 29 Medically Serious Adverse Event in Adjunctive Studies When Numerical Frequency (%) in ≤ 9 yo Patients Is Greater Than the Frequency (%) in ≥ 10 yo Patients During Open-Label Treatment with Any Topiramate Daily Dose

Medically Serious Adverse Event	≤ 2 yo* N = 284	2 – 9 yo N = 453	10 – 15 yo N = 365	≥ 16 yo N = 2909
Cardiac arrest	0.7 %	0.2 %	0 %	0 %
Convulsion aggravated	8.1	3.1	3.3	5.0
Convulsion grand mal	1.4	3.4	3.3	1.5
Encephalopathy	0.7	0	0.3	0.1

Reviewer Comment

- It is difficult to suspect any clear concern for increased risk for these medically serious adverse events based upon this open-label experience with relatively minimal numerical differences in incidence amongst the groups. The incidence of cardiac arrest is based upon 2 cases for the infants/toddlers and one case for the 2-9 year old patients. I am unable to think of any scientifically plausible reason to expect an increased risk for cardiac arrest in very young pediatric patients.

- Although my review did occasionally note an increased incidence for some type of seizure or seizure aggravation in young pediatric patients compared to older pediatric patients or adults, I did not pay much attention to this observation and believe that it was a real signal. The controlled study experience of topiramate treatment for various types of epilepsy in monotherapy or adjunctive therapy does not show a clearly increased risk for seizures from topiramate.

- **Overall, I interpreted my review for medically serious adverse events as suggesting that there is no clear signal for an increased risk for medically serious events in young pediatric patients (≤ 9 years) compared to older patients (≥ 10 years) during topiramate treatment as monotherapy or adjunctive therapy.**

7.3.5 Submission Specific Primary Safety Concerns

Safety Findings of Special Interest

This section includes analyses of topics considered to be of special interest in the pediatric safety profile of topiramate. These topics are growth delay/retardation, metabolic acidosis, hyperammonemia/encephalopathy, oligohidrosis/hyperthermia, renal events including nephrolithiasis, hepatic injury, and visual adverse events. The discussion presented below includes analyses of programmatically generated tables summarizing selected AEs and laboratory data followed by a clinical assessment of the narratives for all pediatric subjects (<16 years of age) with special safety events that were presented.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 30 shows the incidence of TEAEs in various age subgroups according to randomized dose (400 mg or 50 mg groups) in the double-blind phase of Study 106. TEAEs or SOCs that show a numerically greater incidence for the 400 mg group than for the 50 mg group are emphasized by bolding and yellow highlighting.

Table 30 Incidence of TEAEs According to Age Subgroups for 400 mg and 50 mg Randomized Daily Topiramate Dose Groups in Study 106 (TEAEs presented when any age subgroup shows 400 mg group ≥ 2 % and > 50 mg group)

Treatment	TPM 50 mg				TPM 400 mg			
Age (years)	6-9 (N=17)	10-15 (N=57)	6-15 (N=74)	≥ 16 (N=160)	6-9 (N=20)	10-15 (N=57)	6-15 (N=77)	≥ 16 (N=159)
SOC/TEAE	%	%	%	%	%	%	%	%
Body As A Whole - General Disorders	18	11	12	37	30	23	25	35
Allergy	0	0	0	1	0	**2**	1	0
Asthenia	0	0	0	4	0	**4**	**3**	6
Chest Pain	0	2	1	1	0	2	1	**2**
Fever	6	0	1	3	**20**	**9**	**12**	**2**
Leg Pain	0	0	0	2	0	0	0	3
Malaise	0	0	0	1	**5**	0	1	1
Centr & Periph Nerv Syst Disorders	29	39	36	51	10	**40**	32	**59**
Ataxia	0	0	0	3	0	0	0	**4**
Dizziness	0	18	14	13	**5**	11	9	**14**
Hypertonia	0	0	0	0	0	0	0	**3**
Hypoesthesia	0	0	0	4	0	0	0	**5**
Hypokinesia	0	2	1	0	0	0	0	1
Muscle Contractions Involuntary	0	0	0	3	0	**4**	**3**	3
Paresthesia	6	2	3	21	0	**16**	**12**	**40**
Vertigo	0	0	0	4	0	**4**	**3**	3
Gastro-Intestinal System Disorders	29	28	28	34	20	28	26	33
Colitis	0	0	0	0	0	**2**	1	1
Constipation	0	0	0	1	0	0	0	**4**
Diarrhea	18	5	8	6	5	**11**	**9**	6
Flatulence	0	2	1	0	0	0	0	1
Gastritis	0	0	0	0	0	0	0	**3**
Gastroesophageal Reflux	0	0	0	1	0	0	0	2
Hiccup	0	2	1	0	0	0	0	1
Mouth Dry	0	0	0	1	0	0	0	**3**
Saliva Increased	0	0	0	0	**5**	0	**1**	**1**

Treatment	TPM 50 mg				TPM 400 mg			
Age (years)	6-9 (N=17)	10-15 (N=57)	6-15 (N=74)	≥ 16 (N=160)	6-9 (N=20)	10-15 (N=57)	6-15 (N=77)	≥ 16 (N=159)
SOC/TEAE	%	%	%	%	%	%	%	%
Stomatitis Ulcerative	0	0	0	0	0	2	1	0
Tooth Ache	0	0	0	2	0	2	1	1
Tooth Caries	0	0	0	0	0	2	1	1
Hearing And Vestibular Disorders	0	2	1	2	0	0	0	3
Earache	0	2	1	0	0	0	0	1
Liver And Biliary System Disorders	0	0	0	2	0	2	1	3
Gamma-GT Increased	0	0	0	1	0	2	1	3
Metabolic And Nutritional Disorders	6	7	7	11	5	21	17	23
Weight Decrease	6	7	7	6	5	21	17	17
Musculo-Skeletal System Disorders	6	2	3	10	0	2	1	7
Arthritis	0	0	0	2	0	2	1	1
Platelet,Bleeding & Clotting Disorders	0	0	0	2	5	4	4	3
Epistaxis	0	0	0	1	5	4	4	1
Psychiatric Disorders	59	25	32	41	45	46	45	57
Aggressive Reaction	0	0	0	1	5	0	1	0
Anorexia	18	12	14	4	10	14	13	14
Anxiety	0	2	1	4	0	0	0	6
Apathy	0	0	0	0	0	2	1	1
Appetite Increased	0	0	0	1	0	2	1	1
Cognitive Problems NOS	6	0	1	1	5	7	6	4
Confusion	0	0	0	4	5	2	3	4
Depression	0	0	0	7	0	4	3	9
Difficulty With Concentration/Attention	18	4	7	7	15	9	10	8
Difficulty With Memory NOS	6	0	1	6	5	2	3	11
Euphoria	0	0	0	0	0	2	1	1
Insomnia	18	2	5	9	0	4	3	9
Libido Decreased	0	0	0	0	0	0	0	3
Mood Problems	0	2	1	2	0	11	8	5
Nervousness	12	4	5	4	5	5	5	4
Personality Disorder(Behavior Problems)	0	0	0	1	5	2	3	1
Psychomotor Slowing	12	0	3	3	5	0	1	5

Treatment	TPM 50 mg				TPM 400 mg			
Age (years)	6-9 (N=17)	10-15 (N=57)	6-15 (N=74)	≥ 16 (N=160)	6-9 (N=20)	10-15 (N=57)	6-15 (N=77)	≥ 16 (N=159)
SOC/TEAE	%	%	%	%	%	%	%	%
Somnolence	18	11	12	10	15	11	12	15
Red Blood Cell Disorders	0	4	3	1	0	4	3	1
Anemia	0	2	1	1	0	4	3	1
Reproductive Disorders, Female	0	2	1	4	0	2	1	4
Intermenstrual Bleeding	0	0	0	1	0	2	1	1
Resistance Mechanism Disorders	6	5	5	11	20	16	17	13
Herpes Zoster	0	0	0	0	5	0	1	0
Infection	6	2	3	2	10	7	8	3
Infection Bacterial	0	0	0	0	5	0	1	0
Infection Viral	0	4	3	6	0	9	6	8
Respiratory System Disorders	35	30	31	29	30	32	31	26
Bronchitis	0	2	1	3	0	7	5	4
Dyspnea	0	0	0	1	0	0	0	2
Laryngitis	0	0	0	0	0	2	1	0
Pharyngitis	0	14	11	9	5	4	4	4
Rhinitis	12	4	5	2	5	7	6	4
Sinusitis	0	2	1	6	0	5	4	3
Upper Resp Tract Infection	18	16	16	16	20	18	18	13
Skin And Appendages Disorders	12	12	12	9	10	11	10	16
Acne	0	5	4	2	0	0	0	3
Alopecia	0	2	1	3	0	5	4	4
Nail Disorder	0	2	1	0	0	0	0	1
Pruritus	0	0	0	1	0	2	1	4
Rash	12	0	3	1	10	2	4	4
Rash Erythematous	0	2	1	0	0	0	0	1
Skin Discoloration	0	0	0	1	0	2	1	0
Urticaria	0	0	0	1	0	2	1	1
Special Senses Other, Disorders	0	0	0	3	0	0	0	6
Taste Perversion	0	0	0	3	0	0	0	5
Urinary System Disorders	12	2	4	4	5	7	6	11
Cystitis	0	0	0	1	0	2	1	3
Dysuria	0	0	0	0	0	0	0	2
Micturition Frequency	0	0	0	0	0	4	3	2
Renal Calculus	0	0	0	0	0	0	0	3

Treatment	TPM 50 mg				TPM 400 mg			
Age (years)	6-9 (N=17)	10-15 (N=57)	6-15 (N=74)	≥ 16 (N=160)	6-9 (N=20)	10-15 (N=57)	6-15 (N=77)	≥ 16 (N=159)
SOC/TEAE	%	%	%	%	%	%	%	%
Urinary Incontinence	6	0	1	1	5	**2**	**3**	1
Urinary Tract Infection	6	2	3	1	0	0	0	**2**
Vascular (Extracardiac) Disorders	0	0	0	3	**15**	**2**	**5**	1
Flushing	0	0	0	1	**15**	**2**	**5**	1
Vision Disorders	6	2	3	7	0	**4**	3	7
Diplopia	0	0	0	0	0	**2**	**1**	**1**
White Cell And Res Disorders	0	2	1	1	0	2	1	1
Eosinophilia	0	0	0	0	0	**2**	**1**	**1**

Table 31 (derived from Table 30) shows notable TEAEs or SOCs in which the incidence for the 400 mg group was ≥ 3 % the incidence in the 50 mg group for various age subgroups. TEAEs with an increased treatment effect/difference incidence that was ≥ 3 % greater in pediatric patients 6-9 years than in older pediatric patients (10-15 years) or adults are highlighted in yellow and bold type.

Table 31 Notable Topiramate (TPM) Treatment Effects / Differences %) Percentages (TPM 400 mg % - TPM 50 mg for Treatment-Emergent Adverse Events (TEAEs) in Monotherapy Study 400 in Different Age Groups

Treatment	Treatment Effect/Difference % of TPM 400 mg Daily; N=17) (vs 50 mg Daily; N=17)			
Age (years)	6-9 (400 mg, N=20; 50 mg, N=17)	10-15 (400 mg, N=57; 50 mg, N=57)	6-15 (400 mg, N=77; 50 mg, N=74)	≥ 16 (400 mg, N=159; 50 mg, N=160)
SOC/TEAE	%	%	%	%
Body As A Whole - General Disorders				
Fever	**14**	9	11	1
Malaise	**5**	0	2	0
Centr & Periph Nerv Syst Disorders				
Dizziness	**5**	<	<	1
Gastro-Intestinal System Disorders				
Saliva Increased	**5**	0	1	1
Psychiatric Disorders				
Aggressive Reaction	**5**	0	1	<
Confusion	**5**	2	3	0
Personality Disorder(Behavior Problems)	**5**	2	3	0
Resistance Mechanism Disorders	**14**	11	12	2
Herpes Zoster	**5**	0	1	0
Infection Bacterial	**5**	0	1	0
Respiratory System Disorders	<	2	0	<
Pharyngitis	**5**	<	<	<
Vascular (Extracardiac) Disorders	**15**	2	5	<
Flushing	**15**	2	5	0

Notable = Treatment Effect / Difference % for 6-9 yo > 10-15 yo Group % and 16 yo and older Group % by ≥ 3 %
< indicates < 0 % (i.e., TPM 50 mg % > TPM 400 mg %)
SOC presented for reference for specific TEAE within a SOC regardless of %

On the basis of Table 31, the following is a list of specific TEAEs (or SOC TEAEs) occurring notably more frequently (i.e., ≥ 3 % Treatment Difference for 400 mg – 50 mg) in pediatric patients (6-15 yo) than in adults in Study 106.

- Body As A Whole – General Disorders Pediatric (13 %) vs Adult (<)
- Fever Pediatric (11 %) vs Adult (1 %)
- Muscle Contractions Involuntary Pediatric (3 %) vs Adult (0 %)
- Vertigo Pediatric (3 %) vs Adult (<)
- Platelets, Bleeding & Clotting Disorders Pediatric (4 %) vs Adult (1 %)
- Epistaxis Pediatric (4 %) vs Adult (0 %)
- Confusion Pediatric (3 %) vs Adult (0 %)
- Personality Disorder (Behavior Problems) Pediatric (3 %) vs Adult (0 %)
- Resistance Mechanism Disorders Pediatric (12 %) vs Adult (2 %)
- Infection Pediatric (5 %) vs Adult (1 %)
- Bronchitis Pediatric (4 %) vs Adult (1 %)
- Vascular (Extracardiac) Disorders Pediatric (5 %) vs Adult (<)
- Flushing Pediatric (5 %) vs Adult (0 %)

Reviewer Comment

- Several TEAEs (i.e., fever, malaise, dizziness, saliva increased, aggressive reaction, personality disorder-behavior problems, Herpes Zoster, infection bacterial, pharyngitis, flushing) occurred in the youngest pediatric patients (6-9 years)with a treatment difference incidence that exceeded the treatment difference incidence of older pediatric patients and adults by ≥ 3 % (Table 31). Notably, several of these TEAEs (i.e., fever, Herpes Zoster, infection bacterial, pharyngitis) were associated (or at least were possibly associated) with an infection.

- Table 31 also indicated that several TEAEs (i.e., fever, muscle contractions involuntary, vertigo, epistaxis, confusion, personality disorder-behavior problems, infection, bronchitis, flushing) were also more frequent in pediatric patients. I note that the TEAEs of fever, infection, and bronchitis possibly reflect an increased risk for infection. I recognize again that the increased risk may not be completely related to topiramate but may be at least partially related to the generally increased risk for various infections in pediatric patients (vs adults).

- The pathophysiological explanation for an increased risk for flushing in young pediatric patients 6-9 years (vs older pediatric patients and adults and in pediatric patients (vs adults) is not clear.

Adjunctive Treatment Studies

Despite the fact that the safety experience in the randomized, double-blind, placebo-controlled studies for adjunctive treatment involved relatively low topiramate exposures (typically targeting 6 mg/kg/day and also lower daily dosing) compared to the projected exposures (6 - 22 mg/kg/day) for monotherapy in young pediatric patients 2-9 years.

I have reviewed the adjunctive studies and will comment on adverse events that appeared to be more frequent in patients ≤ 9 yo) than on older pediatric patients (10-15 years) and adults (≥ 16 years). More specifically, my review focused on determining whether the incidence of certain TEAEs (based upon the

treatment difference of Topiramate % - Placebo %) are more frequent in young pediatric patients 2-9 years compared to that in older pediatric patients 10-15 years and adults (> 16 years). I have noted TEAEs that occurred more frequently in patients 2-9 years by a ≥ 3 % treatment difference.

In the pooled, placebo-controlled adjunctive studies, the 2-9 year old group consisted of 53 treated with placebo and of 50 treated with topiramate (target 6 mg/kg/day), the 10 – 15 year old group consisted of 45 treated with placebo and of 47 treated with topiramate (target 6 mg/kg/day), and the adults consisted of 386 treated with placebo and of 817 treated with topiramate (any dose = 200, 400, 600, 800, or 1000 mg daily randomized dose). These analyses represented a comparison across studies. The following TEAEs were more common (≥ 3 % treatment difference) in patients 2-9 years than in patients 10-15 years or adults : insomnia, personality disorder (behavior problem), alopecia, dermatitis, urinary incontinence, and thrombocytopenia.

In Study YP, that was the trial that served as the basis for obtaining approval of topiramate for adjunctive treatment of partial epilepsy, the 2-9 year old group consisted of 23 treated with placebo and of 22 treated with topiramate (target 6 mg/kg/day), and the 10 – 15 year old group consisted of 22 treated with placebo and of 18 treated with topiramate (target 6 mg/kg/day). The following TEAEs were more common (≥ 3 % treatment difference) in patients 2-9 years than in patients 10-15 years : fatigue, rhinitis, hyperkinesis, hyporeflexia, purpura, and urinary incontinence.

Reviewer Comment

- Amongst the TEAEs that appeared to be more frequent in adjunctive patients 2-9 years than in older pediatric patients (10-15 years) or in adults, the only TEAE(s) that occurred more commonly in the 400 mg daily group vs the 50 mg daily group of young patients 6-9 years in the key monotherapy Study 106 was personality disorder (behavior problems).

- Of interest, the treatment difference for urinary continence in Study 106 for young patients 6-9 years was not increased. However, the treatment difference for urinary incontinence appeared to be more common in patients 2-9 years in the adjunctive studies. In Study YP, treatment difference for urinary incontinence was 13 % for patients 2-9 yeas and 0 % for patients 10-15 years. In the pooled adjunctive studies, the treatment difference for urinary incontinence was 4 % in patients 2-9 years and 0 % in patients 10-15 years and in adults. The topiramate label shows a treatment difference of 2 % for urinary incontinence for pediatric patients 2-16 years.

  It appears that urinary continence may be a particular adverse risk in very young pediatric patients and consideration should be given to noting this in the label.

Adjunctive Treatment for Partial Onset Epilepsy in Infants and Toddlers (1 to 24 months)

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. In a single randomized, double-blind, placebo-controlled investigational trial, the efficacy, safety, and tolerability of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent antiepileptic drug therapy in infants 1 to 24 months of age with refractory partial onset seizures were assessed. After 20 days of double-blind treatment, topiramate (at fixed doses of 5, 15, and 25 mg/kg/day) did not demonstrate efficacy compared with placebo in controlling seizures.

In general, the adverse reaction profile in this population was similar to that of older pediatric patients, although results from the above controlled study and an open-label, long-term extension study in these infants/toddlers (1 to 24 months old) suggested some adverse reactions/toxicities(not previously observed in older pediatric patients and adults; i.e., growth/length retardation, certain clinical laboratory abnormalities, and other adverse reactions/toxicities that occurred with a greater frequency and/or greater severity than had been recognized previously from studies in older pediatric patients or adults for various indications.

These very young pediatric patients appeared to experience an increased risk for infections (any topiramate dose 12%, placebo 0%) and of respiratory disorders (any topiramate dose 40%, placebo 16%). **The following adverse reactions were observed in at least 3% of patients on topiramate and were 3% to 7% more frequent than in patients on placebo: viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection, cough, and bronchospasm. A generally similar profile was observed in older children.**

Open Label, Long-Term Safety Experience (i.e., TEAEs) from "Extension" Studies

The controlled, monotherapy and adjunctive treatment clinical trial experiences were very limited for assessing safety at topiramate daily doses that were thought to be relevant to the topiramate dosing exposures expected with recommended daily topiramate dosing for monotherapy in patients 2-9 years (based upon review of the pharmacometric analyses in this NDA). Consequently, this safety review redirected its attention toward assessing the safety of treating patients 2-9 years with topiramate monotherapy based upon the safety (e.g., especially TEAEs) of treating young pediatric patients (i.e., $\leq$ 9 years, consisting of analyses of separate populations 1-24 months and 2-9 years) with topiramate in adjunctive, open-label, extension trials and in monotherapy, open-label trials in which relatively high doses of topiramate were used. The following analyses present the results of TEAEs, SAEs, and TEAEs causing study discontinuation according to various age subgroups, various, topiramate modal daily dose ranges for monotherapy and adjunctive therapy, and also according whether or not a concomitant enzyme-inducing AED (EIAED) that can decrease topiramate exposure by approximately 50 % was being used in the adjunctive trials. This reviewer's analyses focused on the incidence of TEAEs primarily when TEAEs reflected an occurrence in a subgroup for 2 or more patients and there was a treatment difference for the incidence of TEAEs amongst different age subgroups for a specific dose range. **Treatment differences in these open-label study analyses were summarized and presented when the incidence of a TEAE in a young pediatric population (i.e., < 2 years OR 2-9 years) was at least 3 % (or more) greater than the incidence of the respective TEAE in the older pediatric patients (10-15 years) AND adults for each respective topiramate dose category/range.**

Monotherapy

Initially, the pharmacometric review suggested that recommended dosing would be approximately 7-13 mg/kg/day with dosing recommendations being inversely related to weight for pediatric patients 2-9 years. The target Cmin (median) for topiramate for the lower limit dosing recommendation was approximately 8 µg/ml. Consequently, the open-label, extension studies analyzed TEAEs relative to the following modal daily dose ranges : < 7, $\geq$ 7, 7-13, > 13 mg/kg/day, and any dose. Table 32 shows an example of the monotherapy analyses for TEAEs.

TEAEs

Initially, the frequency of TEAEs in various topiramate modal dose ranges between young pediatric patients (6-9 years) and older patients (10-15 years and adults) were compared. Table 33 shows results for TEAEs that occurred more frequently in young pediatric patients (6-9 years) compared to older patients in the various, topiramate modal dosing categories. More specifically, Table 33 shows results for a treatment difference of at least 3 % or greater in pediatric patients 6-9 years compared to TEAEs in older pediatric patients (10-15 years) **and** in adults (≥ 16 years) for various, monotherapy modal, daily doses.

These TEAEs that appeared to occur more frequently in young pediatric patients (6-9 years) were evaluated to determine whether there was a suggestion of topiramate dose response by assessing the corresponding frequency of each TEAE in able 31 for a dose-response. A dose-response was suggested for a specific TEAE if the frequency of TEAEs in there was a greater frequency in the ≥ 7 mg/kg/day group or the 7-13 mg/kg/day group or the > 13 mg/kg group compared to one or more of the lower dose groups. TEAEs that suggested a dose-response included anemia, cognitive problems (NOS), fever, nervousness, and rhinitis.

Table 32 Monotherapy Open-Label Extension Trials: TEAE by Modal Dose Group and Age Group

Modal Dose (mg/kg/day)	< 7								≥ 7							
Age (years)	6- 9 (n = 16)		10- 15 (n= 43)		6- 15 (n= 59)		≥ 16 (n= 268)		6- 9 (n = 25)		10- 15 (n= 69)		6- 15 (n= 94)		≥ 16 (n= 79)	
TEAE	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ALCOHOL INTOLERANCE	0		0		0		1	0.4	0		0		0		0	
ALLERGIC REACTION	0		1	2.3	1	1.7	7	2.6	0		0		0		0	
ALLERGY	0		0		0		2	0.7	0		0		0		1	1.3
ALLERGY AGGRAVATED	0		0		0		0		0		0		0		1	1.3
ALOPECIA	0		0		0		5	1.9	0		0		0		1	1.3
AMENORRHOEA	0		0		0		1	0.4	0		0		0		0	
ANAEMIA	0		0		0		5	1.9	2	8	2	2.9	4	4.3	1	1.3
ANAEMIA B TWELVE DEFICIENCY	0		0		0		1	0.4	0		0		0		0	
ANAEMIA HYPOCHROMIC	1	6.3	0		1	1.7	1	0.4	0		0		0		1	1.3
ANDROGEN DEFICIENCY	0		0		0		0		0		0		0		1	1.3
ANGINA PECTORIS	0		0		0		0		1	4	0		1	1.1	0	
ANOREXIA	2	12.5	0		2	3.4	11	4.1	1	4	0		1	1.1	10	12.7

Modal Dose (mg/kg/day)	7- 13								> 13							
Age (years)	6- 9 (n = 15)		10- 15 (n= 62)		6- 15 (n= 77)		≥ 16 (n= 75)		6- 9 (n = 10)		10- 15 (n= 7)		6- 15 (n= 17)		≥ 16 (n= 4)	
TEAE	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ALCOHOL INTOLERANCE	0		0		0		0		0		0		0		0	
ALLERGIC REACTION	0		0		0		0		0		0		0		0	
ALLERGY	0		0		0		1	1.3	0		0		0		0	
ALLERGY AGGRAVATED	0		0		0		1	1.3	0		0		0		0	
ALOPECIA	0		0		0		1	1.3	0		0		0		0	
AMENORRHOEA	0		0		0		0		0		0		0		0	
ANAEMIA	0		2	3.2	2	2.6	1	1.3	2	20	0		2	11.8	0	
ANAEMIA B TWELVE DEFICIENCY	0		0		0		0		0		0		0		0	
ANAEMIA HYPOCHROMIC	0		0		0		1	1.3	0		0		0		0	
ANDROGEN DEFICIENCY	0		0		0		0		0		0		0		1	25
ANGINA PECTORIS	1	6.7	0		1	1.3	0		0		0		0		0	
ANOREXIA	1	6.7	0		1	1.3	9	12	0		0		0		1	25

Trials included in data summaries: open-label, extension phases of TOPMAT-EPMN-104 and TOPMAT-EPMN-106. Modal dose is based on open-label exposure.

Table 33 Increased Treatment Difference * Incidence of TEAEs (i.e., ≥ 3 % Difference) in Pooled, Open-Label Monotherapy Studies of Young Pediatric Patients (6-9 years)
According to Various, Modal Topiramate Daily Doses When Incidence for a Modal Dose Was ≥ 3 % Greater Than Incidence in Older Pediatric Patients (10-15 years) AND Adults (≥ 16 years)

Preferred Term TEAE	Modal Topiramate Dose (mg/kg/day)				
	< 7 N=16	≥ 7 N=25	7 – 13 N=15	> 13 N=10	Any
Anemia		+		+	
Cognitive problems (NOS)		+	+		+
Fever		+		+	+
Gastroenteritis	+				
Headache	+				+
Infection viral	+				+
Nervousness		+			
Otitis media	+				+
Pharyngitis	+				+
Rhinitis		+	+	+	+
Sinusitis	+				+
Upper respiratory tract infection	+		+		+
Vomiting	+		+		+

*Treatment difference is presented when the incidence of a TEAE in a young pediatric population (i.e., < 2 years OR 2-9 years) was at least 3 % (or more) greater than the incidence of the respective TEAE in the older pediatric patients (10-15 years) AND adults for each respective topiramate dose category/range

Reviewer Comment

- Although no TEAEs in Table 33 stood out as being a unique adverse reaction from topiramate in the young pediatric patients treated with topiramate monotherapy, several TEAE appeared to occur more frequently in young pediatric patients compared to older pediatric and adult patients.

- **It is interesting to note that several of the TEAEs in Table 33 suggested an increased risk for infection (i.e., infection viral, otitis media, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection) related to topiramate treatment. I believe that these infections are at least partially related to topiramate treatment despite the fact that I recognize that various infections, in general, are more common in pediatric patients than in adults and in younger pediatric patients compared to older pediatric patients.**

SAEs

There were no SAEs that were more frequent (i.e., ≥ 3 %) in pediatric patients 6-9 years compared to SAEs in older pediatric patients (10-15 years) or in adults.

TEAEs Causing Study Discontinuation

There were no TEAEs causing study discontinuation that were more frequent (i.e., ≥ 3 %) in pediatric patients 6-9 years compared to SAEs in older pediatric patients (10-15 years) or in adults.

Adjunctive Therapy

Initially, the pharmacometric review suggested that the upper limit of the targeted Cmin for topiramate would be approximately 13 µg/ml (e.g., median Cmin). Of interest and of potential relevance, a pediatric pharmacokinetic (PK) study had shown that infants and toddlers (1-24 months) treated with 15 mg/kg/day topiramate had mean Cmin of approximately 13 µg/ml. Consequently, the open-label, extension studies analyzed TEAEs relative to the following modal daily dose ranges : < 15, ≥ 15, 15-30, > 30 mg/kg/day, and any topiramate dose. Considering that one or more EIAEDs can decrease topiramate levels by approximately 50 %, it was hypothesized that a 30 mg/kg/day dose of topiramate taken with a concomitant EIAED would result in similar exposure as a pediatric patient taking 15 mg/kg/day without any concomitant EIAED. Table 34 shows an example of the adjunctive therapy analyses for patients not taking any concomitant EIAED. Corresponding tables for patients NOT taking any concomitant EIAED were similar.

TEAEs

Initially, the frequency of TEAEs in various topiramate modal dose ranges between young pediatric populations of patients (≤ 2 years, and 2-9 years) and older pediatric patients (10-15 years) and adults were compared. Table 35 shows results for TEAEs that occurred more frequently in one or both young pediatric groups of patients compared to older patients in the various, topiramate modal dosing categories without any concomitant EIAED. More specifically, Table 35 shows results for a treatment difference of at least 3 % or greater in pediatric patients ≤ 2 years or 2-9 years compared to TEAEs in older pediatric patients (10-15 years) **and** in adults (≥ 16 years) for various, adjunctive modal, daily doses.

These TEAEs that appeared to occur more frequently in young pediatric patients (≤ 9 years) were evaluated to determine whether there was a suggestion of topiramate dose response by assessing the corresponding frequency of each TEAE in Table 35 for a dose-response relationship. A dose-response relationship was suggested for a specific TEAE if the frequency of TEAEs was a greater frequency in the ≥ 15 mg/kg/day group or the 15-30 mg/kg/day group or the > 30 mg/kg group compared to one or more of the lower dose groups. In the youngest patients (≤ 2 years), TEAEs that suggested a dose-response relationship included acidosis, dehydration, infection viral, gastroenteritis, and vomiting. In the pediatric patients 2-9 years, TEAEs that suggested a dose-response relationship included acidosis, ceullitis, dehydration, infection viral, gastroenteritis, otitis media, pneumonia, rhinitis, somnolence, and vomiting.

Table 36 shows results for TEAEs that occurred more frequently in one or both young pediatric groups of patients compared to older patients in the various, topiramate modal dosing categories for patients taking at least one concomitant EIAED. More specifically, Table 36 shows results for a treatment difference of at least 3 % or greater in pediatric patients ≤ 2 years or 2-9 years compared to TEAEs in older pediatric patients (10-15 years) **and** in adults (≥ 16 years) for various, adjunctive modal, daily doses.

These TEAEs that appeared to occur more frequently in young pediatric patients (≤ 9 years) were evaluated to determine whether there was a suggestion of topiramate dose response by assessing the corresponding frequency of each TEAE in Table 36 for a dose-response relationship. A dose-response relationship was suggested for a specific TEAE if the frequency of TEAEs was a greater frequency in the ≥ 15 mg/kg/day group or the 15-30 mg/kg/day group or the > 30 mg/kg group compared to one or more of the lower dose groups. In the youngest patients (≤ 2 years), TEAEs that suggested a dose-response relationship included acidosis, anorexia, gastroenteritis, hypokalemia, pharyngitis, and pneumonia. In the

Table 34 Adjunctive Treatment of Epilepsy Open-Label Extension Trials: TEAE by Modal Dose and Age for Subjects NOT Taking Concomitant EIAED

Modal Dose (mg/kg/day)	< 15												≥ 15											
Age (years)	≤ 2		2- 5		6- 9		2- 9		10- 15		6- 15		≥ 16		≤ 2		2- 5		6- 9		2- 9		10- 15		6- 15		≥ 16	
	n= 23		n= 110		n= 125		n= 235		n= 138		n= 263		n= 648		n = 81		n= 11		n= 21		n= 32		n= 14		n= 35		n= 74	
TEAE	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Abdomen Enlarged	0		0		0		0		0		0		2	0.3	0		0		0		0		0		0		0	
Abdominal Pain	0		6	5.5	7	5.6	13	5.5	7	5.1	14	5.3	63	9.7	1	1.2	0		0		0		1	7.1	1	2.9	16	21.6
Abscess	0		0		1	0.8	1	0.4	2	1.4	3	1.1	4	0.6	0		1	9.1	0		1	3.1	0		0		1	1.4
Accommodation Abnormal	0		0		0		0		0		0		2	0.3	0		0		0		0		0		0		0	
Acidosis	6	26.1	0		0		0		0		0		1	0.2	26	32.1	0		0		0		0		0		0	
Acne	0		0		1	0.8	1	0.4	4	2.9	5	1.9	17	2.6	0		0		0		0		1	7.1	1	2.9	7	9.5
Adverse Event Nos	0		5	4.5	5	4	10	4.3	6	4.3	11	4.2	10	1.5	1	1.2	1	9.1	4	19	5	15.6	0		4	11.4	4	5.4
Aggressive Reaction	0		3	2.7	10	8	13	5.5	6	4.3	16	6.1	24	3.7	0		3	27.3	0		3	9.4	4	28.6	4	11.4	1	1.4
Agitation	0		1	0.9	2	1.6	3	1.3	5	3.6	7	2.7	11	1.7	1	1.2	3	27.3	3	14.3	6	18.8	1	7.1	4	11.4	3	4.1
Albuminuria	0		0		0		0		1	0.7	1	0.4	2	0.3	0		0		0		0		0		0		0	

Modal Dose (mg/kg/day)	15- 30												> 30											
Age (years)	≤ 2		2- 5		6- 9		2- 9		10- 15		6- 15		≥ 16		≤ 2		2- 5		6- 9		2- 9		10- 15		6- 15		≥ 16	
	n = 46		n= 9		n= 21		n= 30		n= 13		n= 34		n= 68		n = 35		n= 2		n= 0		n= 2		n= 1		n= 1		n= 6	
TEAE	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Abdomen Enlarged	0		0		0		0		0		0		0		0		0		0		0		0		0		0	
Abdominal Pain	0		0		0		0		1	7.7	1	2.9	13	19.1	1	2.9	0		0		0		0		0		3	50
Abscess	0		1	11.1	0		1	3.3	0		0		1	1.5	0		0		0		0		0		0		0	
Accommodation Abnormal	0		0		0		0		0		0		0		0		0		0		0		0		0		0	
Acidosis	10	21.7	0		0		0		0		0		0		16	45.7	0		0		0		0		0		0	
Acne	0		0		0		0		0		0		7	10.3	0		0		0		0		1	100	1	100	0	
Adverse Event Nos	0		1	11.1	4	19	5	16.7	0		4	11.8	3	4.4	1	2.9	0		0		0		0		0		1	16.7
Aggressive Reaction	0		2	22.2	0		2	6.7	4	30.8	4	11.8	1	1.5	0		1	50	0		1	50	0		0		0	
Agitation	1	2.2	3	33.3	3	14.3	6	20	1	7.7	4	11.8	3	4.4	0		0		0		0		0		0		0	
Albuminuria	0		0		0		0		0		0		0		0		0		0		0		0		0		0	

Trials included in data summaries: ABS-001, COGF-001, EPAJ-111, EPPD-001, EPPD-002, IP, M215, M216, M218, MET-001, MS220, YEP, YET, YC, YH, YI, YJ, YK, YKE, YKP, YKT, YLT, YLTE, YOL, YOLE, YZL, YZT, YZW, OL extension of YF, YG, YP, YTC, YTCE, YL. TOPMAT-EPMN-1002 and TOPMAT-EPMN-3001. Modal dose is based on open-label exposure.

Table 35 Increased Treatment Difference *Incidence of TEAEs (i.e., ≥ 3 % Difference) in **Pooled, Open-Label Adjunctive Treatment Studies (NOT TAKING ANY CONCOMITANT EIAED) of Young Pediatric Patients (≤ 2 years and/or 2-9 years)** According to Various, Modal Topiramate Daily Doses When Incidence for a Modal Dose Was ≥ 3 % Greater Than Incidence in Older Pediatric Patients (10-15 years) AND Adults (≥ 16 years)

Preferred Term TEAE	Modal Topiramate Dose (mg/kg/day) ≤ 2 years					Modal Topiramate Dose (mg/kg/day) 2–9 years				
	< 15 N=23	≥ 1 N=81	15 – 30 N=46	> 30 N=35	Any	< 15 N=235	≥ 15 N=32	15 – 30 N=30	> 30 N=2	Any
Acidosis										
Anemia	+	+	+	+	+					
Bronchitis					+					
Cellulitis					+					
Dehydration							+	+		
Diarrhea		+			+		+			+
Fever					+	+	+			
Gastroenteritis					+	+	+			+
Infection viral	+				+		+	+		+
Insomnia	+			+	+	+				+
Otitis media				+			+			
Personality disorder (Behavior problems)						+				
Pneumonia										+
Renal calculus	+	+	+	+	+	+	+	+		+
Rhinitis		+	+							
Somnolence				+			+	+		
Upper respiratory tract infection				+			+	+		
Vomiting					+					
	+			+		+				+

*Treatment difference is presented when the incidence of a TEAE in a young pediatric population (i.e., < 2 years OR 2-9 years) was at least 3 % (or more) greater than the incidence of the respective TEAE in the older pediatric patients (10-15 years) AND adults **for each respective topiramate dose category/range.**

Table 36 Increased Treatment Difference* Incidence of TEAEs (i.e., ≥ 3 % Difference) in Pooled, Open-Label Adjunctive Treatment Studies (TAKING AT LEAST 1 CONCOMITANT EIAED) of Young Pediatric Patients (≤ 2 years and/or 2-9 years) According to Various, Modal Topiramate Daily Doses When Incidence for a Modal Dose Was ≥ 3 % Greater Than Incidence in Older Pediatric Patients (10-15 years) AND Adults (≥ 16 years)

Preferred Term TEAE	Modal Topiramate Dose (mg/kg/day) ≤ 2 years					Modal Topiramate Dose (mg/kg/day) 2–9 years				
	< 15 N=155	≥ 15 N=125	15 – 30 N=80	> 30 N=45	Any	< 15 N=160	≥ 15 N=26	15 – 30 N=23	> 30 N=3	Any
Acidosis										
Anemia	+	+	+	+	+					
Anorexia		+						+		
Bronchitis										
Constipation	+				+		+			+
Epistaxis										
Gait abnormal							+	+		
Gastroenteritis							+	+		
Hypokalemia	+						+			
Infection	+ +						+	+		
Infection viral										
Insomnia	+ +	+		+		+	+	+		
Moniliasis								+		
Nervousness	+ +						+	+		
Otitis media										
Pharyngitis	+					+		+	+	
Pneumonia	+		+	+		+	+	+	+	
Rhinitis		+	+	+ +			+	+	+	
Upper respiratory tract infection	+ +									
Vomiting									+	

*Treatment difference is presented when the incidence of a TEAE in a young pediatric population (i.e., < 2 years OR 2-9 years) was at least 3 % (or more) greater than the incidence of the respective TEAE in the older pediatric patients (10-15 years) AND adults for each respective topiramate dose category/range.

pediatric patients 2-9 years, TEAEs that suggested a dose-response relationship included anemia, bronchitis, epistaxis, gait abnormal, gastroenteritis, hypokalemia, infection viral, insomnia, monoliasis, otitis media, pharyngitis, pneumonia, upper respiratory tract infection, and vomiting.

Reviewer Comment

- Although TEAEs in Table 35 and Table 36 did not stand out as being a unique adverse reaction from topiramate in the young pediatric patients treated with topiramate monotherapy, many TEAE appeared to occur more frequently in young pediatric patients compared to older pediatric and adult patients.

- The one TEAE that showed markedly increased frequency in infants/toddlers (1-24 months) compared to older pediatric patients (2-9, and 10- 15 years) and adults was "acidosis" presumably reflecting the well known effect of topiramate-induced carbonic inhibition resulting in metabolic acidosis. Although the frequency of metabolic acidosis (a laboratory based diagnosis), which is dose-dependent and often asymptomatic, is common to all ages of patients even at relatively low topiramate daily dosing, I believe that the increased frequency is most likely related to increased awareness of the frequency of subnormal serum bicarbonate/metabolic acidosis observed during the infant/toddler studies. When all the other monotherapy and adjunctive studies were conducted, the high frequency of topiramate-induced metabolic acidosis was not a well recognized adverse reaction and little to no attention was directed toward serum bicarbonate measurements. Considering that decreased serum bicarbonate below the normal reference range (i.e., metabolic acidosis is often asymptomatic, detection of metabolic acidosis by adverse events is an insensitive and non-specific means for suspecting metabolic acidosis.

- Many of the TEAEs that showed an increased frequency in young pediatric patients compared to older pediatric patients and adults were common to the tables (i.e., Table 33, Table 35, Table 36) for monotherapy and adjunctive therapy (with or without an EIAED). More specifically, anemia, gastroenteritis, infection viral, otitis media, rhinitis, upper respiratory tract infection, and vomiting were common to all three tables. TEAEs occurring in the open-label monotherapy and adjunctive therapy (without EIAED) experience were fever, Fever was common to the monotherapy and adjunctive therapy experience without an EIAED, and pharyngitis was common to the monotherapy and adjunctive therapy experience with an EIAED. TEAEs occurring in both adjunctive tables (without and with an EIAED) were bronchitis, dehydration, diarrhea, insomnia, and pneumonia.

- **As observed in the monotherapy experience in Table 33, it is clearly noteworthy that several of the TEAEs in Table 35 and/or Table 36 suggested an increased risk for infection (i.e., infection viral, pneumonia, infection, otitis media, pharyngitis, rhinitis, upper respiratory tract infection, cellulitis, bronchitis, diarrhea, gastroenteritis related to topiramate treatment.**

- An increased risk for infections (i.e., viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection) from topiramate treatment has previously been recognized in the randomized, double-blind, placebo-controlled study of infants/toddlers (patients 1-24 months) and is currently noted in the pediatric section of the label.

- The current topiramate label shows an increased treatment difference (topiramate – Placebo) incidence for TEAEs of pneumonia, and infection viral for pediatric patients (2-16 years) compared to adult patients. This label also shows an increased treatment difference (400 mg daily topiramate – 50 mg daily topiramate) incidence for TEAEs of infection, infection viral, upper respiratory tract infection, rhinitis, and bronchitis in pediatric patients (10-15 years) compared to adults.

- Considering the total body of evidence of the current label, the reviews conducted for this NDA, and the placebo-controlled experience in infant/toddlers, I believe that topiramate treatment clearly causes an increased risk for infections. This risk is greater in pediatric patients (especially in younger pediatric patients) than in adults. **I also believe that the various lines of evidence suggesting a topiramate-related increased risk for infections (especially in "young" pediatric patients (≤ 9 years) should be explicitly noted in a paragraph in the adverse reactions section of the label.**

- It is of interest to note that there were some TEAEs (e.g., paresthesia) that seemed to occur with decreased incidence/frequency in the open-label experience for young pediatric patients (most notably for patients ≤ 2 years) compared to the frequency in older pediatric patients or adults. Although I have no proof for my hypothetical explanation of this phenomenon, I do not think that it is reasonably likely that these adverse reactions were not experienced with a decreased frequency in young pediatric patients. Instead, I believe that some of these TEAEs were not captured as an adverse event because of problems/difficulties/limitations in the communication of the adverse reactions by the young patient. Many of these TEAEs observed in the open-label experience are subjective symptoms and not surprisingly, young pediatric patients are not typically able or capable of communicating some symptoms reflecting adverse events/reactions. This of course is a limitation of any study of very young pediatric patients.

SAEs

There was an increased frequency (≥ 3 %) of SAEs for pneumonia in the youngest patients (≤ 2 years) and in the young patients 2-9 years treated with topiramate without any concomitant EIAED compared to older pediatric patients (10-15 years) and adults for the topiramate modal daily dose of > 15 mg/kg/day and 15-30 mg/kg/day dose ranges. This increased risk was dose-related in the 2-9 patients but not in the patients 2 years and younger.

There was also an increased frequency (≥ 3 %) of SAEs for bronchitis, diarrhea, fever, and dehydration a in the youngest patients (≤ 2 years) treated with topiramate without any concomitant EIAED compared to older pediatric patients (10-15 years) and adults for any topiramate modal daily dose.

Compared to older pediatric patients (10-15 years) and adults, there was an increased frequency (≥ 3 %) of SAEs for pneumonia in the youngest patients (≤ 2 years) treated with topiramate with at least one concomitant EIAED at < 15, and > 30 mg/kg/day. Using the same older subgroups of patients for comparison, there was an increased frequency (≥ 3 %) of SAEs for pneumonia in the young pediatric patients 2-9 years treated with topiramate with at least one concomitant EIAED for the ≥ 15, 15-30, and > 30 mg/kg/day dose groups. This increased risk was dose-related for both young populations.

There was also an increased frequency (≥ 3 %) of SAEs for pneumonia, and infection viral in the youngest patients (≤ 2 years) treated with topiramate with at least one concomitant EIAED compared to older pediatric patients (10-15 years) and adults for any topiramate modal daily dose

Reviewer Comment

- These analyses of SAEs clearly indicated an increased risk for pneumonia in the very young pediatric patients (≤ 2 years and 2-9 years) as an SAE and an increased risk for infection viral in the youngest pediatric subgroup ((≤ 2 years).

- This topiramate related increased risk for serious adverse reactions of pneumonia and infection viral is striking along with the increased risk for many non serious infections already noted.

TEAEs Causing Study Discontinuation

There were no TEAEs causing study discontinuation that were more frequent (i.e., ≥ 3 %) in pediatric patients 6-9 years compared to SAEs in older pediatric patients (10-15 years) or in adults for any adjunctive experience (i.e., with and without concomitant EIAED).

7.4.2 Laboratory Findings

Because many laboratory centers (with different corresponding normal ranges) have been used for topiramate studies over time, a harmonized set of normal ranges and markedly abnormal criteria were applied across all studies and indications.

Among all the analyses of clinical laboratory analytes, the only clinical laboratory results/analysis worthy of note were those for serum bicarbonate reflecting various time perspectives on the frequency and severity of decreased serum bicarbonate reflecting metabolic acidosis in various age subgroups and according to various daily topiramate doses. .

The bicarbonate analyses presented are those for the indication of monotherapy of epilepsy and adjunctive therapy of epilepsy. Because analyses for migraine prophylaxis and treatment of bipolar disorder involved relatively low topiramate daily dosing that was not very relevant to the topiramate exposure projected for pediatric patients in this NDA, these analyses were not presented nor discussed despite the fact that topiramate treatment for these indications reflected notable risk for metabolic acidosis of various severities.

The incidence analysis is provided for the following scenarios: at any visit, at final visit, at final visit and any previous post-baseline visit, at 2 consecutive visits, and at 2 consecutive visits or final visit. Only counts and percentages that are non-zero in at least one treatment group are presented within each age group. The denominator is the number of subjects with at least one post-baseline serum bicarbonate measurement in the DB phase from the corresponding treatment and age group.

Double-blind, Controlled Monotherapy Study 106

Table 37 shows the frequency of decreased serum bicarbonate (< 20 mEq/L) reflecting metabolic acidosis with different time perspectives in the double-blind phase of the pivotal, monotherapy epilepsy studies according to age subgroups and randomized, daily topiramate dose. It is relevant to note that the randomized doses in the 6-9 year old patients in columns reflecting 25/50 mg or 200/500 mg doses were the low doses (e.g., 25 or 200 mg) in these groups and not the higher doses (50 mg or 500 mg).

Table 38 shows the frequency of "markedly abnormal" serum bicarbonate (i.e., < 17 mEq/L and decrease from baseline of > 5 mEq/ml when serum bicarbonate was ≥ 20 mEq/ml at baseline) reflecting metabolic acidosis with different time perspectives in the double-blind phase of the pivotal, monotherapy epilepsy studies according to age subgroups and randomized, daily topiramate dose.

Table 39 shows the frequency of decreased serum bicarbonate (< 20 mEq/L) reflecting metabolic acidosis with different time perspectives in the double-blind phase of the key pivotal, monotherapy epilepsy study (# 106) according to age subgroups and randomized, daily topiramate doses (50 mg or 400 mg).

Table 40 shows the frequency of "markedly abnormal" serum bicarbonate (i.e., < 17 mEq/L and decrease from baseline of > 5 mEq/ml when serum bicarbonate was ≥ 20 mEq/ml at baseline) in the same age subgroup populations for the same time perspectives in Study 106.

Table 37 Incidence of Treatment-Emergent Serum Bicarbonate Values < 20 mEq/L for the Pooled Double-Blind Phase of the Epilepsy Monotherapy Studies (104, 105, 106)

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	TPM 25/50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	TPM 400 mg/day n (%)	TPM 200/500 mg/day n (%)
Age 6-9	25	6	8	20	7
At any visit	12 (48)	4 (67)	6 (75)	10 (50)	6 (86)
At final visit	0	1 (17)	3 (38)	6 (30)	3 (43)
At final visit and any previous post-baseline visit	0	1 (17)	3 (38)	5 (25)	1 (14)
At 2 consecutive visits	6 (24)	2 (33)	4 (50)	6 (30)	3 (43)
At 2 consecutive visits or final visit	6 (24)	2 (33)	4 (50)	8 (40)	5 (71)
Age 10-15	70	19	16	57	7
At any visit	14 (20)	4 (21)	10 (63)	15 (26)	6 (86)
At final visit	5 (7)	0	5 (31)	5 (9)	3 (43)
At final visit and any previous post-baseline visit	3 (4)	0	2 (13)	5 (9)	2 (29)
At 2 consecutive visits	2 (3)	1 (5)	2 (13)	11 (19)	5 (71)
At 2 consecutive visits or final visit	7 (10)	1 (5)	6 (38)	11 (19)	6 (86)
Age >=16	264	170	166	158	113
At any visit	74 (28)	55 (32)	57 (34)	63 (40)	63 (56)
At final visit	29 (11)	14 (8)	18 (11)	27 (17)	24 (21)
At final visit and any previous post-baseline visit	10 (4)	5 (3)	8 (5)	21 (13)	14 (12)
At 2 consecutive visits	18 (7)	16 (9)	26 (16)	31 (20)	33 (29)
At 2 consecutive visits or final visit	42 (16)	26 (15)	37 (22)	39 (25)	45 (40)
Age 6-15	95	25	24	77	14
At any visit	26 (27)	8 (32)	16 (67)	25 (32)	12 (86)
At final visit	5 (5)	1 (4)	8 (33)	11 (14)	6 (43)
At final visit and any previous post-baseline visit	3 (3)	1 (4)	5 (21)	10 (13)	3 (21)
At 2 consecutive visits	8 (8)	3 (12)	6 (25)	17 (22)	8 (57)
At 2 consecutive visits or final visit	13 (14)	3 (12)	10 (42)	19 (25)	11 (79)

Table 38 Incidence of Treatment-Emergent Serum Bicarbonate Values < 17 mEq/L With a Decrease of > 5 mEq/L from Baseline When the Baseline Serum Bicarbonate was ≥ 20 mEq/L for the Pooled Double-Blind Phase of the Epilepsy Monotherapy Studies (104, 105, 106)

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	TPM 25/50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	TPM 400 mg/day n (%)	TPM 200/500 mg/day n (%)
Age 6-9	25	6	8	20	7
At any visit	4 (16)	0	2 (25)	2 (10)	4 (57)
At final visit	0	0	0	0	1 (14)
At 2 consecutive visits	0	0	1 (13)	2 (10)	0
At 2 consecutive visits or final visit	0	0	1 (13)	2 (10)	1 (14)
Age 10-15	70	19	16	57	7
At any visit	2 (3)	0	4 (25)	6 (11)	3 (43)
At final visit	1 (1)	0	3 (19)	2 (4)	1 (14)
At final visit and any previous post-baseline visit	0	0	0	1 (2)	0
At 2 consecutive visits	0	0	0	1 (2)	0
At 2 consecutive visits or final visit	1 (1)	0	3 (19)	3 (5)	1 (14)
Age >=16	264	170	166	158	113
At any visit	7 (3)	7 (4)	8 (5)	22 (14)	6 (5)
At final visit	2 (1)	3 (2)	1 (1)	8 (5)	2 (2)
At final visit and any previous post-baseline visit	0	0	0	3 (2)	1 (1)
At 2 consecutive visits	0	0	0	4 (3)	1 (1)
At 2 consecutive visits or final visit	2 (1)	3 (2)	1 (1)	9 (6)	3 (3)
Age 6-15	95	25	24	77	14
At any visit	6 (6)	0	6 (25)	8 (10)	7 (50)
At final visit	1 (1)	0	3 (13)	2 (3)	2 (14)
At final visit and any previous post-baseline visit	0	0	0	1 (1)	0
At 2 consecutive visits	0	0	1 (4)	3 (4)	0
At 2 consecutive visits or final visit	1 (1)	0	4 (17)	5 (6)	2 (14)

Table 39 **Incidence of Treatment-Emergent Serum Bicarbonate Values < 20 mEq/L for the Pooled Double-Blind Phase of Epilepsy Monotherapy Study 106**

Age Group Analysis Visits	TPM 50 mg/day n (%)	TPM 400 mg/day n (%)	Total TPM n (%)
Age 6-9	17	20	37
At any visit	6 (35)	10 (50)	16 (43)
At final visit	0	6 (30)	6 (16)
At final visit and any previous post-baseline visit	0	5 (25)	5 (14)
At 2 consecutive visits	1 (6)	6 (30)	7 (19)
At 2 consecutive visits or final visit	1 (6)	8 (40)	9 (24)
Age 10-15	57	57	114
At any visit	10 (18)	15 (26)	25 (22)
At final visit	5 (9)	5 (9)	10 (9)
At final visit and any previous post-baseline visit	3 (5)	5 (9)	8 (7)
At 2 consecutive visits	1 (2)	11 (19)	12 (11)
At 2 consecutive visits or final visit	6 (11)	11 (19)	17 (15)
Age >=16	160	158	318
At any visit	41 (26)	63 (40)	104 (33)
At final visit	16 (10)	27 (17)	43 (14)
At final visit and any previous post-baseline visit	4 (3)	21 (13)	25 (8)
At 2 consecutive visits	9 (6)	31 (20)	40 (13)
At 2 consecutive visits or final visit	23 (14)	39 (25)	62 (19)
Age 6-15	74	77	151
At any visit	16 (22)	25 (32)	41 (27)
At final visit	5 (7)	11 (14)	16 (11)
At final visit and any previous post-baseline visit	3 (4)	10 (13)	13 (9)
At 2 consecutive visits	2 (3)	17 (22)	19 (13)
At 2 consecutive visits or final visit	7 (9)	19 (25)	26 (17)

Table 40 **Incidence of Treatment-Emergent Serum Bicarbonate Values < 17 mEq/L With a Decrease of > 5 mEq/L from Baseline When the Baseline Serum Bicarbonate was ≥ 20 mEq/L for Double-Blind Epilepsy Monotherapy Study 106**

Age Group Analysis Visits	TPM 50 mg/day n (%)	TPM 400 mg/day n (%)	Total TPM n (%)
Age 6-9	17	20	37
At any visit	2 (12)	2 (10)	4 (11)
At 2 consecutive visits	0	2 (10)	2 (5)
At 2 consecutive visits or final visit	0	2 (10)	2 (5)
Age 10-15	57	57	114
At any visit	2 (4)	6 (11)	8 (7)
At final visit	1 (2)	2 (4)	3 (3)
At final visit and any previous post-baseline visit	0	1 (2)	1 (1)
At 2 consecutive visits	0	1 (2)	1 (1)
At 2 consecutive visits or final visit	1 (2)	3 (5)	4 (4)
Age >=16	160	158	318
At any visit	5 (3)	22 (14)	27 (8)
At final visit	2 (1)	8 (5)	10 (3)
At final visit and any previous post-baseline visit	0	3 (2)	3 (1)
At 2 consecutive visits	0	4 (3)	4 (1)
At 2 consecutive visits or final visit	2 (1)	9 (6)	11 (3)
Age 6-15	74	77	151
At any visit	4 (5)	8 (10)	12 (8)
At final visit	1 (1)	2 (3)	3 (2)
At final visit and any previous post-baseline visit	0	1 (1)	1 (1)
At 2 consecutive visits	0	3 (4)	3 (2)
At 2 consecutive visits or final visit	1 (1)	5 (6)	6 (4)

Reviewer Comment

- In general, the frequency of metabolic acidosis for all daily doses of topiramate for most time perspectives (Table 37) is greatest in the youngest pediatric patients (6-9 years) compared to this frequency in older pediatric patients (10-15 years) and adults (≥ 16 years) in the pooled, pivotal monotherapy trials.

- In the pooled pivotal monotherapy trials, the frequency of "markedly abnormal" decreased serum bicarbonate (i.e., more severe metabolic acidosis) was usually greatest in the youngest pediatric patients 6-9 years, occasionally similar to the frequency in older pediatric patients (10-15 years) and typically greater than that in adults (Table 38).

- Regarding the daily dose (400 mg) and time perspective (serum bicarbonate < 20 mEq/L at 2 consecutive visits or the final visit; what we commonly term "persistent" metabolic acidosis) of greatest interest, the frequency of metabolic acidosis was highest (40 %) in the youngest pediatric patients (6-9 years) compared to the frequency in older pediatric patients 10-15 years (19 %), and in adults (25 %) (Table 39).

- For 2 consecutive visits or final visit, the incidence of "markedly abnormal" serum bicarbonate decrease (i.e., < 17 mEq/L and decrease from baseline of > 5 mEq/ml when serum bicarbonate was $\geq$ 20 mEq/ml at baseline) was greatest (10 %) in youngest pediatric patients than the incidence in older pediatric patients (5 %) or in adults (6 %) (Table 40). This incidence of abnormality in older pediatric patients was similar to that in adults.

Pooled Double-blind, Placebo-Controlled Adjunctive Treatment Studies

Table 41 shows the frequency of decreased serum bicarbonate (< 20 mEq/L) reflecting metabolic acidosis with different time perspectives in the double-blind phase of the pooled, adjunctive treatment studies according to age subgroups and randomized, daily topiramate dose.

Table 42 shows the frequency of "markedly abnormal" serum bicarbonate (i.e., < 17 mEq/L and decrease from baseline of > 5 mEq/ml when serum bicarbonate was $\geq$ 20 mEq/ml at baseline) reflecting metabolic acidosis with different time perspectives in the pooled, double-blind phase of the pivotal, adjunctive treatment studies according to age subgroups and randomized, daily topiramate dose.

Table 41 **Incidence of Treatment-Emergent Serum Bicarbonate Values < 20 mEq/L for the Pooled Double-Blind Phase of the Adjunctive Therapy Studies (YP, YTC, YTCE, YL, YD, and YE)**

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 6 mg/kg/day n (%)	TPM 200 mg/day n (%)	TPM 400 mg/day n (%)
Age 2-5	22	21	0	0
At any visit	7 (32)	18 (86)	0	0
At final visit	5 (23)	16 (76)	0	0
At final visit and any previous post-baseline visit	4 (18)	16 (76)	0	0
At 2 consecutive visits	1 (5)	15 (71)	0	0
At 2 consecutive visits or final visit	5 (23)	16 (76)	0	0
Age 6-9	31	29	0	0
At any visit	7 (23)	21 (72)	0	0
At final visit	3 (10)	17 (59)	0	0
At final visit and any previous post-baseline visit	2 (6)	13 (45)	0	0
At 2 consecutive visits	2 (6)	13 (45)	0	0
At 2 consecutive visits or final visit	3 (10)	18 (62)	0	0
Age 10-15	44	42	0	0
At any visit	6 (14)	34 (81)	0	0
At final visit	4 (9)	22 (52)	0	0
At final visit and any previous post-baseline visit	2 (5)	17 (40)	0	0
At 2 consecutive visits	1 (2)	17 (40)	0	0
At 2 consecutive visits or final visit	4 (9)	26 (62)	0	0
Age 2-9	53	50	0	0
At any visit	14 (26)	39 (78)	0	0
At final visit	8 (15)	33 (66)	0	0
At final visit and any previous post-baseline visit	6 (11)	29 (58)	0	0
At 2 consecutive visits	3 (6)	28 (56)	0	0
At 2 consecutive visits or final visit	8 (15)	34 (68)	0	0
Age 2-15	97	92	0	0
At any visit	20 (21)	73 (79)	0	0
At final visit	12 (12)	55 (60)	0	0
At final visit and any previous post-baseline visit	8 (8)	46 (50)	0	0
At 2 consecutive visits	4 (4)	45 (49)	0	0
At 2 consecutive visits or final visit	12 (12)	60 (65)	0	0
Age >=16	65	0	5	57
At any visit	2 (3)	0	2 (40)	28 (49)
At final visit	1 (2)	0	2 (40)	14 (25)
At final visit and any previous post-baseline visit	0	0	2 (40)	9 (16)
At 2 consecutive visits	0	0	2 (40)	14 (25)
At 2 consecutive visits or final visit	1 (2)	0	2 (40)	19 (33)

Table 42 **Incidence of Treatment-Emergent Serum Bicarbonate Values < 17 mEq/L With] a Decrease of > 5 mEq/L from Baseline When the Baseline Serum Bicarbonate was ≥ 20 mEq/L L for the Pooled Double-Blind Phase of the Adjunctive Therapy Studies (YP, YTC, YTCE, YL, YD, and YE)**

Age Group Analysis Visits	Placebo n (%)	TPM 6 mg/kg/day n (%)	TPM 200 mg/day n (%)	TPM 400 mg/day n (%)
Age 2-5	22	21	0	0
At any visit	1 (5)	5 (24)	0	0
At final visit	0	3 (14)	0	0
At final visit and any previous post-baseline visit	0	1 (5)	0	0
At 2 consecutive visits	0	2 (10)	0	0
At 2 consecutive visits or final visit	0	4 (19)	0	0
Age 6-9	31	29	0	0
At any visit	0	2 (7)	0	0
Age 10-15	44	42	0	0
At any visit	0	9 (21)	0	0
At final visit	0	4 (10)	0	0
At final visit and any previous post-baseline visit	0	1 (2)	0	0
At 2 consecutive visits	0	3 (7)	0	0
At 2 consecutive visits or final visit	0	6 (14)	0	0
Age >=16	65	0	5	57
At any visit	0	0	0	3 (5)
At final visit	0	0	0	1 (2)
At 2 consecutive visits	0	0	0	1 (2)
At 2 consecutive visits or final visit	0	0	0	2 (4)
Age 2-9	53	50	0	0
At any visit	1 (2)	7 (14)	0	0
At final visit	0	3 (6)	0	0
At final visit and any previous post-baseline visit	0	1 (2)	0	0
At 2 consecutive visits	0	2 (4)	0	0
At 2 consecutive visits or final visit	0	4 (8)	0	0
Age 2-15	97	92	0	0
At any visit	1 (1)	16 (17)	0	0
At final visit	0	7 (8)	0	0
At final visit and any previous post-baseline visit	0	2 (2)	0	0
At 2 consecutive visits	0	5 (5)	0	0
At 2 consecutive visits or final visit	0	10 (11)	0	0

Reviewer Comment

- Overall, the incidence of metabolic acidosis for the various time perspectives was generally quite similar for the absolute incidence and the treatment difference incidence (Topiramate % - Placebo %) of topiramate-treated patients (~ 6 mg/kg./day) for young pediatric patients (2-9 years) and older pediatric patients (10-15 years) in the pooled, randomized, double-blind, placebo-controlled studies for adjunctive treatment. In one instance (i.e., any visit), the treatment difference was mildly greater for older pediatric patients, in two instances (i.e., final visit and any previous visit, and 2 consecutive visits) the treatment difference was mildly greater for younger pediatric patients, and in two instances (i.e., final visit, and 2 consecutive visits or final visit) the treatment difference was essentially the same (Table 41). All pediatric patients received the same target dose.

- For comparison, results are shown for adults who were randomized to receive either 200 or 400 mg topiramate daily in pooled, randomized, double-blind, placebo-controlled studies for adjunctive treatment. Although only 5 patients received 200 mg, a significant number of patients received placebo (N=65) or 400 mg (N=57). The treatment difference incidences (for different time perspectives) in pediatric patients 2-9 years were notably greater than the respective incidences adults (Table 41).

- Treatment difference incidences in very young pediatric patients (2-5 years) were either similar to or greater or moderately greater than respective treatment difference incidences for pediatric patients 6-9 years, suggesting perhaps a somewhat increased sensitivity for these youngest patients (Table 41).

- The treatment difference incidences indicating markedly abnormal serum bicarbonate reductions for metabolic acidosis for the various time perspectives were not remarkably different but were quite similar for younger pediatric patients (2-9 years) and older pediatric patients (10-15 years) in the adjunctive studies (Table 42).

- The 2-9 year old group of patients who showed metabolic acidosis was primarily composed of young patients 2-5 years old. Correspondingly, when one compares results for 2-5 year old patients with those of 10-15 year old patients, the treatment different incidences are similar (Table 42).

Open Label, Long-Term Safety Experience Incidence of Serum Bicarbonate Decreases (i.e., Metabolic Acidosis) from "Extension" Studies

During our review, we recognized that the safety assessment for monotherapy of topiramate for 2-9 year old patients would not only need to rely primarily on open-label extension study safety from adjunctive trials (i.e., a different indication than the one under review), but also on a different aged population (i.e., 1-24 months). I have noted previously (and reviewed these results) that safety assessments for TEAEs in these open-label studied were reviewed for making the overall safety assessment. In addition, considering the well-known adverse reaction of topiramate for producing metabolic acidosis, it was of interest to assess what was the effect of topiramate on producing metabolic acidosis in these trials for the various dose ranges and age subgroups. Consequently, we requested that the sponsor submit similar analyses as had been conducted for TEAEs for monotherapy and adjunctive therapy in the open-label trials for various threshold abnormalities in reducing serum bicarbonate for the various, modal topiramate daily doses and for the various age subgroups. More specifically, the sponsor conducted analyses for the incidence of a serum bicarbonate decrease < 20, < 17, < 15, and < 17 mEq/L AND decrease > 5 mEq/L from baseline for patients with a serum bicarbonate at baseline of > 20 mEq/L. These analyses also showed the incidence of the various serum bicarbonate decreases reflecting metabolic acidosis from various time perspectives including at : 1) any visit; 2) any visit excluding final visit; 3) any 2 consecutive

visits; and 4) any 2 consecutive visits or final visit. Previously, we have considered the time perspective of "2 consecutive visits or final visit to be an important time perspective for the development of metabolic acidosis and have also considered this occurrence to represent "persistent" metabolic acidosis.

I reviewed all of these analyses, but will focus on presenting results showing the incidence of new onset metabolic acidosis (i.e., serum bicarbonate < 20 mEq/L) and new onset more severe metabolic acidosis (i.e., serum bicarbonate < 17 mEq/L AND decrease > 5 mEq/L from baseline).

Monotherapy and Adjunctive Therapy

Table 43 and Table 44 shows the incidence of "persistent" metabolic acidosis in the open-label, monotherapy and adjunctive therapy extension studies for any notable decrease < 20 mEq/L and for markedly abnormal reductions. My focus was on comparing results in young pediatric patients (≤ 2 years, 2-9 years, < 9 years) compared to those for older pediatric patients (10-15 years) and adults (> 16 years). I have highlighted and bolded results for young pediatric patients that were appeared to be notable because they were numerically greater than results for older pediatric patients and adults.

Table 43 Incidence of "Persistent" Metabolic Acidosis* in Pooled, Open-Label, Monotherapy Extension Studies According to Age Subgroups and Modal Topiramate (TPM) Daily Dose

TPM Modal Dose and Serum Bicarbonate Abnormality	6 – 9 yo	10 – 15 yo	≥ 16 yo
TPM Modal Dose < 7 mg/kg/day			
N	14	41	259
< 20 mEq/L	**57**	34	32
< 17 and > 5 mEq/L decrease from baseline	0	7	5
TPM Modal Dose ≥ 7 mg/kg/day			
N	24	67	77
< 20 mEq/L	21	7	32
< 17 and > 5 mEq/L decrease from baseline	**8**	0	3
TPM Modal Dose 7 - 13 mg/kg/day			
N	14	60	73
< 20 mEq/L	29	7	29
< 17 and > 5 mEq/L decrease from baseline	**7**	0	3
Modal Dose > 13 mg/kg/day			
N	10	7	4
< 20 mEq/L	10	14	100
< 17 and > 5 mEq/L decrease from baseline	**10**	0	0
Any TPM Modal Dose			
N	38	108	336
< 20 mEq/L	34	18	32
< 17 and > 5 mEq/L decrease from baseline	5	3	4

*"Persistent" metabolic Acidosis=Specific threshold bicarbonate decrease for 2 consecutive visits or final visit

Table 44 Incidence of "Persistent" Metabolic Acidosis* in Pooled, Open-Label, Adjunctive Therapy Extension Studies According to Age Subgroups and Modal Topiramate (TPM) Daily Dose

TPM Modal Dose and Serum Bicarbonate Abnormality	NOT EIAED Concomitant AED					EIAED Concomitant AED					ANY Concomitant AED				
	≤ 2* yo	2 – 9 yo	≤ 9 yo	10-15 yo	≥ 16 yo	≤ 2* yo	2 – 9 yo	≤ 9 yo	10-15 yo	≥ 16 yo	≤ 2* yo	2 – 9 yo	≤ 9 yo	10-15 yo	≥ 16 yo
TPM Modal Dose < 15 mg/kg/day															
N	18	158	176	101	145	38	113	151	129	392	56	271	327	230	537
< 20 mEq/L	**50**	34	36	41	32	**39**	35	36	34	28	**43**	35	36	37	29
< 17 and > 5 mEq/L decrease from baseline	**22**	7	9	10	4	5	4	5	5	2	**11**	6	7	7	2
TPM Modal Dose ≥ 15 mg/kg/day															
N	59	24	83	12	46	102	20	122	20	114	161	44	205	32	160
< 20 mEq/L	66	79	70	83	63	61	**65**	61	60	38	63	**73**	65	69	45
< 17 and > 5 mEq/L decrease from baseline	17	21	18	17	13	**18**	**25**	**19**	5	4	**17**	**23**	**19**	9	6
TPM Modal Dose 15 - 30 mg/kg/day															
N	36	23	59	11	41	62	17	79	18	106	98	40	138	10	147
< 20 mEq/L	64	78	69	82	61	53	59	54	61	37	57	70	61	69	44
< 17 and > 5 mEq/L decrease from baseline	11	17	14	18	12	**10**	**24**	**13**	6	4	10	**20**	13	10	6
TPM Modal Dose > 30 mg/kg/day															
N	23	1	24	1	5	40	3	43	2	8	63	4	67	3	113
< 20 mEq/L	70	100	71	100	80	**73**	**100**	**74**	50	50	**71**	**100**	**73**	67	62
< 17 and > 5 mEq/L decrease from baseline	**26**	**100**	**29**	0	20	**30**	**33**	**30**	0	0	**29**	**50**	**30**	0	8
Any TPM Modal Dose															
N	77	182	259	113	191	140	133	273	149	506	217	315	532	262	697
< 20 mEq/L	**62**	40	**47**	45	39	**55**	**40**	**48**	38	30	**58**	40	**47**	41	33
< 17 and > 5 mEq/L decrease from baseline	**18**	9	12	11	6	**14**	8	**11**	5	2	**16**	8	**11**	7	3

*"Persistent" metabolic Acidosis=Specific threshold bicarbonate decrease for 2 consecutive visits or final visit

Reviewer Comment

- In the open-label, monotherapy experience, there were some notable differences (increased incidence for youngest patients) for the incidence of "persistent" metabolic acidosis of any severity (< 20 mEq/L) serum bicarbonate) or moderately severe (< 17 and > 5 mEq/L decrease from baseline serum bicarbonate) "persistent" metabolic acidosis for 6-9 year old patients compared to older patients (10-15 years and adults) (Table 43). The incidence of any "persistent" metabolic acidosis was much higher for patients 6-9 vs both groups of older patients for the lowest, modal topiramate daily dose range (< 7 mg/kg/day) . This result also showed that the development of "persistent" metabolic acidosis is very common (57 %) in these youngest patients.

  The other notable differences were related to moderately severe, "persistent" metabolic acidosis and occurred for higher modal topiramate dosing (> 7, 7-13, and > 13 mg/kg/day). These results suggest an increased sensitivity for developing moderately severe "persistent" metabolic acidosis in these youngest patients.

- For patients not taking a concomitant EIAED, there was a remarkably increased incidence of any and moderately severe "persistent" metabolic acidosis in the youngest pediatric patients (1-24 months) receiving a modal, topiramate daily dose of < 15 mg/kg/day compared to older pediatric patients (2-9 years, and 10-15 years) and adults. **Of significant relevance to this sNDA, the incidence of any and moderately severe "persistent" metabolic acidosis in patients 2-9 year was similar to the incidences in older pediatric patients and adults.**

- For patients not taking a concomitant EIAED and the highest, modal topiramate daily dose range (> 30 mg/kg/day), the incidence of moderately severe "persistent" metabolic acidosis in the youngest pediatric patients (1-24 months) and in the 2-9 year old patients was numerically greater than the incidences for older pediatric patients and adults (Table 44). However, the number of patients included in the analyses of all separate age subgroups (2-9, 10-15, $\geq$ 16 years) was very small making the percentages unreliable. The only age subgroup that contained a significant number of patients and suggested that its percentage (26 %) was reliable was for the youngest pediatric patients 1-24 months (i.e., $\leq$ 2 years).

  Of additional interest, the incidence of moderately severe "persistent" metabolic acidosis was similar for the youngest pediatric patients (1-24 months) at the highest dose range (> 30 mg/kg/ml) and at the lowest dose range (< 15 mg/kg/day). Because these results did not suggest any dose-dependent effect for these dose ranges, it appeared that maximal inhibition of carbonic anhydrase may have occurred at dosing < 15 mg/kg/day. Considering that previous data have suggested that some carbonic anhydrase inhibition can occur at relatively low topiramate daily doses and that this pharmacological effect is dose-dependent, it is likely that analyses of lower dose ranges would have been necessary to show dose-dependent effects.

- For patients taking at least one concomitant EIAED, the incidence of moderately severe "persistent" metabolic acidosis was notably greater for young pediatric patients (1-24 months, and 2-9 years) treated with a modal, topiramate daily dose of $\geq$ 15 mg/kg/day (including 15-30, and > 30 mg/kg/day) compared to older pediatric patients (10-15 years) and adults (Table 44). Furthermore, higher incidences for > 30 mg/kg/day for each age subgroup compared to 15-30 mg/kg/day suggested a dose-dependent effect. It was thought that topiramate exposures in patients taking at least one concomitant EIAED would be approximately 50 % lower for each dose range than exposures in patients in the same dose range but not taking any concomitant EIAED.

- Results for "any concomitant AED" (Table 44) combine results from "not EIAED concomitant AED," and "EIAED concomitant AED."

- Results for the incidence of more severe metabolic acidosis (i.e., serum bicarbonate < 15 mEq/L when baseline was ≥ 20 mEq/L) were generally fairly similar for all age subgroups, with respect to conditions (e.g., with or without EIAED) and modal, topiramate daily dose ranges. In particular, I note that incidence results for the most severely decreased bicarbonate analyzed in pediatric patients 2-9 years were relatively similar and not clearly different from incidence results in older pediatric patients and in adults. In some instances, not surprisingly, incidence results for the youngest pediatric patients (1-24 months) were greater than those for older patients.

- **Overall, all these results from the monotherapy and adjunctive therapy open-label treatment experiences (Table 43 and Table 44)were fairly reassuring that the incidence of any severity or moderately severe metabolic acidosis was not a tremendously higher risk for young pediatric patients (2-9 years) compared to the risk in older pediatric patients (10-15 years) and in adults during treatment with relatively high daily doses of topiramate over the long-term. Given that topiramate-induced metabolic acidosis is a well-known and well-characterized adverse reaction, these results support the perspective that exposing patients 2-9 years to the recommended daily dosing of topiramate for monotherapy would not necessarily result in a unique or clearly greater risk compared to the risks expected/anticipated.**

Adjunctive Treatment for Partial Onset Epilepsy in Infants and Toddlers (1 to 24 months)

The following language (shown below here in italics) abstracted from the current topiramate label (section 8.4 Pediatrics) describes the various clinical laboratory abnormalities that were observed in a randomized, double-blind, placebo-controlled study in which very young pediatric patients (i.e., infants/toddlers : 1-24 months) were randomized to placebo or one of three fixed doses of topiramate : 5, 15, 25 mg/kg/day and treated for a relatively short time (20 days).

Topiramate resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5%, placebo 0%), BUN (any topiramate dose 3%, placebo 0%), and protein (any topiramate dose 34%, placebo 6%), and an increased incidence of decreased potassium (any topiramate dose 7%, placebo 0%). This increased frequency of abnormal values was not dose-related. Creatinine was the only analyte showing a noteworthy increased incidence (topiramate 25 mg/kg/day 5%, placebo 0%) of a markedly abnormal increase [see Warnings and Precautions (5.13)]. The significance of these findings is uncertain.

Topiramate treatment also produced a dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10% for 5 mg/kg/day, 9% for 15 mg/kg/day, 14% for 25 mg/kg/day, and 11% for any topiramate dose [see Warnings and Precautions (5.13)]. There was a mean dose-related increase in alkaline phosphatase. The significance of these findings is uncertain.

Topiramate produced a dose-related increased incidence of treatment-emergent hyperammonemia.

Reviewer Comment

- There was no clear suggestion form the review of the various clinical laboratory results for any other unique, adverse clinical laboratory risk for young pediatric patients 2-9 years.

- In particular, review of various analyses for hyperammonemia from open-label, long-term, adjunctive topiramate treatment (at high dose ranges) of the youngest pediatric patients (1-24 months) did not suggest a unique risk for hyperammonemia in pediatric patients 2-9 years who would be treated with the recommended dosing for monotherapy.

7.4.3 Vital Signs (VS = Blood Pressure and Pulse) Body Weight, Height and Body Mass Index (BMI)

Vital Signs (VS – Blood Pressure and Pulse)

The vital sign measurements included diastolic and systolic blood pressure, pulse, and temperature. This section presents descriptive summaries of vital sign values and changes from baseline, as well as the incidence of subjects with abnormal values for diastolic and systolic blood pressure (sitting) and pulse.

Standing and supine systolic and diastolic blood pressure data were collected in epilepsy adjunctive studies Y1, Y2, Y3, YD, and YE, which enrolled adult subjects. Sitting blood pressure was collected for all other studies (note that in study TOPMAT-MIG-3006, position was not specified, and blood pressure data from this study are treated as sitting).
Temperature was collected in the double-blind epilepsy adjunctive therapy studies (except for studies YP, YL, and YTC/YTCE, which enrolled pediatric subjects), migraine prophylaxis study TOPMAT-MIG-3006, and the bipolar disorder study. In most of these studies, the method of obtaining temperature was not specified in the protocol.

The key monotherapy study 106 did not consistently collect blood pressure and pulse measurements in all patients. There were no measurements in the majority of patients in each dose group (400 or 50 mg daily) in all the age subgroups (6-9, 10-15, $\geq$ 16 years). In particular, there were only data at the end of the trial in 6 of 20 patients in the 400 mg group and in 4 of 17 patients in the youngest pediatric patients (6-9 years).

Table 45 and Table 46 show results for mean change from baseline for systolic and diastolic blood pressure for various age subgroups with high and low dose topiramate in monotherapy Study 106.

Table 47 and Table 48 show outlier results for "abnormal" systolic and diastolic blood pressure for various age subgroups with high and low dose topiramate in monotherapy Study 106.

Table 45 Change from Baseline for Sitting Systolic Blood Pressure (SBP) at End of Monotherapy Epilepsy Study 106

Analysis Set: Double-blind Subjects

	TPM 50 mg/day					TPM 400 mg/day				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
DB ENDPOINT										
N	4	11	59	15	74	6	14	77	20	97
Mean	6.75	1.73	-2.44	3.07	-1.32	14.50	-2.14	-1.94	2.85	-0.95
SD	5.852	10.725	18.898	9.736	17.519	20.628	11.935	13.948	16.452	14.538
Median	7.00	0.00	0.00	2.00	0.00	10.00	-2.50	0.00	0.00	0.00
Minimum	0.0	-15.0	-70.0	-15.0	-70.0	-8.0	-20.0	-40.0	-20.0	-40.0
Maximum	13.0	20.0	45.0	20.0	45.0	50.0	19.0	30.0	50.0	50.0

Table 46 Change from Baseline for Sitting Diastolic Blood Pressure (DBP) at End of Monotherapy Epilepsy Study 106

Analysis Set: Double-blind Subjects

	TPM 100 mg/day					TPM 200 mg/day				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
DB ENDPOINT										
N	7	22	177	29	206	8	21	169	29	198
Mean	-3.00	-0.27	-1.00	-0.93	-0.99	0.63	-2.52	-1.44	-1.66	-1.47
SD	4.583	12.548	12.042	11.135	11.893	9.365	7.795	12.196	8.208	11.680
Median	-2.00	0.00	0.00	0.00	0.00	-1.00	0.00	0.00	0.00	0.00
Minimum	-10.0	-32.0	-70.0	-32.0	-70.0	-11.0	-14.0	-32.0	-14.0	-32.0
Maximum	4.0	22.0	30.0	22.0	30.0	20.0	18.0	48.0	20.0	48.0

Table 47 Incidence of Abnormal Sitting Systolic Blood Pressure (SBP) at End of Monotherapy Epilepsy Study 106

Age Group Abnormal Flag	TPM 50 mg/day n/N (%)	TPM 400 mg/day n/N (%)
Sitting Systolic Blood Pressure		
DB Endpoint		
Age 6-9		
SBP value > 120 mmHg (for 6-9 years)	0/4	1/6 (17)
SBP Increase from pre-trt baseline => 10 mmHg (for 2-15 years)	2/4 (50)	4/6 (67)
SBP Increase from pre-trt baseline => 20 mmHg	0/4	2/6 (33)
SBP Increase from pre-trt baseline => 40 mmHg	0/4	1/6 (17)
Age 10-15		
SBP value < 90 mmHg (for => 10 years)	1/11 (9)	0/14
SBP Increase from pre-trt baseline => 10 mmHg (for 2-15 years)	2/11 (18)	3/14 (21)
SBP Increase from pre-trt baseline => 20 mmHg	1/11 (9)	0/14
SBP Decrease from pre-trt baseline => 10 mmHg (for 2-15 years)	2/11 (18)	6/14 (43)
SBP Decrease from pre-trt baseline => 20 mmHg	0/11	1/14 (7)
Age >=16		
SBP value > 130 mmHg (for => 10 years)	12/59 (20)	12/77 (16)
SBP Increase from pre-trt baseline => 20 mmHg	5/59 (8)	5/77 (6)
SBP Increase from pre-trt baseline => 40 mmHg	1/59 (2)	0/77
SBP Decrease from pre-trt baseline => 20 mmHg	9/59 (15)	11/77 (14)
SBP Decrease from pre-trt baseline => 40 mmHg	2/59 (3)	1/77 (1)
Age 6-15		
SBP value > 120 mmHg (for 6-9 years)	0/15	1/20 (5)
SBP value < 90 mmHg (for => 10 years)	1/15 (7)	0/20
SBP Increase from pre-trt baseline => 10 mmHg (for 2-15 years)	4/15 (27)	7/20 (35)
SBP Increase from pre-trt baseline => 20 mmHg	1/15 (7)	2/20 (10)
SBP Increase from pre-trt baseline => 40 mmHg	0/15	1/20 (5)
SBP Decrease from pre-trt baseline => 10 mmHg (for 2-15 years)	2/15 (13)	6/20 (30)
SBP Decrease from pre-trt baseline => 20 mmHg	0/15	1/20 (5)

Table 48 **Incidence of Abnormal Sitting Diastolic Blood Pressure (SBP) at End of Monotherapy Epilepsy Study 106**

Age Group Abnormal Flag	TPM 50 mg/day n/N (%)	TPM 400 mg/day n/N (%)
Sitting Diastolic Blood Pressure		
DB Endpoint		
Age 6-9		
DBP value > 75 mmHg (for 6-9 years)	0/4	1/6 (17)
DBP Increase from pre-trt baseline => 7 mmHg (for 2-15 years)	1/4 (25)	2/6 (33)
DBP Increase from pre-trt baseline => 10 mmHg	1/4 (25)	1/6 (17)
DBP Increase from pre-trt baseline => 20 mmHg	0/4	1/6 (17)
DBP Decrease from pre-trt baseline => 7 mmHg (for 2-15 years)	0/4	1/6 (17)
DBP Decrease from pre-trt baseline => 10 mmHg	0/4	1/6 (17)
Age 10-15		
DBP Increase from pre-trt baseline => 7 mmHg (for 2-15 years)	4/11 (36)	2/14 (14)
DBP Increase from pre-trt baseline => 10 mmHg	4/11 (36)	2/14 (14)
DBP Increase from pre-trt baseline => 20 mmHg	1/11 (9)	0/14
DBP Decrease from pre-trt baseline => 7 mmHg (for 2-15 years)	2/11 (18)	5/14 (36)
DBP Decrease from pre-trt baseline => 10 mmHg	2/11 (18)	5/14 (36)
DBP Decrease from pre-trt baseline => 20 mmHg	1/11 (9)	0/14
Age >=16		
DBP value > 80 mmHg (for => 10 years)	14/59 (24)	10/77 (13)
DBP Increase from pre-trt baseline => 10 mmHg	6/59 (10)	11/77 (14)
DBP Increase from pre-trt baseline => 20 mmHg	1/59 (2)	1/77 (1)
DBP Decrease from pre-trt baseline => 10 mmHg	18/59 (31)	17/77 (22)
DBP Decrease from pre-trt baseline => 20 mmHg	4/59 (7)	4/77 (5)
Age 6-15		
DBP value > 75 mmHg (for 6-9 years)	0/15	1/20 (5)
DBP Increase from pre-trt baseline => 7 mmHg (for 2-15 years)	5/15 (33)	4/20 (20)
DBP Increase from pre-trt baseline => 10 mmHg	5/15 (33)	3/20 (15)
DBP Increase from pre-trt baseline => 20 mmHg	1/15 (7)	1/20 (5)
DBP Decrease from pre-trt baseline => 7 mmHg (for 2-15 years)	2/15 (13)	6/20 (30)
DBP Decrease from pre-trt baseline => 10 mmHg	2/15 (13)	6/20 (30)
DBP Decrease from pre-trt baseline => 20 mmHg	1/15 (7)	0/20

Reviewer comment

- Based upon very limited data, there were no clearly notable/remarkable changes for topiramate on blood pressure in the 6-9 year monotherapy pediatric patients compared to older pediatric patients (10-15 years) and to adults. Neither were the notable/remarkable effects of topiramate on pulse in these same patients.

Body Weight, Height, and Body Mass Index (BMI)

Summaries of body weight values, absolute changes, and percent changes from baseline were presented for subjects of all ages. Other analyses in this section, including height, height velocity, and BMI analyses and weight analyses using Z-score conversions, include only those subjects < 16 years at the time of study entry. Height velocity values (measured in cm/year) and associated Z-scores were computed for each post-baseline year in the study.

No post-baseline height or BMI data are available in the double-blind epilepsy adjunctive studies (including YP, YL, and YTC/YTCE); in the double-blind epilepsy monotherapy study TOPMAT-EPMN-104 or in the double-blind and open-label phases of Study TOPMAT-EPMN-105; or in the migraine prophylaxis study CAPSS-122. Individual study analyses were not performed for studies that had only a few pediatric subjects.

A small number of uncorrected data entry errors exist in the individual study databases (i.e., invalid values which in most cases appear to result from inconsistent application of unit conversion factors).

These outliers, which occurred in a small number of patients at few study visits. The sponsor note that these adjusted results not impact the median values reported without adjustments.

The incidence of AEs related to growth delay or retardation (including weight loss reported as a TEAE) and the number and percentage of subjects with special safety events related to growth delay or retardation based on TEAE criteria and/or growth parameter criteria (i.e., changes in body weight or height Z-scores of 1 unit or more) were discussed.

All analyses of height/height velocity, body weight, and BMI were conducted regardless of serum bicarbonate, with associated "low" serum bicarbonate (i.e., at least 2 post-treatment serum bicarbonate < 20 mEq/L), and without associated "low" serum bicarbonate.

Analyses in open-label (OL) or open-label + double-blind (DB) were conducted for "total" topiramate dose (without respect to dose).

Numerous analyses of body weight, height, and BMI over time were presented for absolute measurements, change from baseline, % change from baseline, percentiles, change from baseline in percentiles, Z scores, and change from baseline Z scores. Subgroup analyses were also conducted with respect to patients having a "low" serum bicarbonate (i.e., such patients had at least 2 post-baseline values of serum bicarbonate < 20 mEq/L) or "not low" serum bicarbonate.

I have summarized what I consider to be notable results in the monotherapy and adjunctive therapy studies.

Monotherapy

- The mean treatment difference (400 mg – 50 mg result) for the Z score change from baseline for body weight was not increased in pediatric patients 6-9 years old (- 0.05) compared to that in older pediatric patients 10-15 years (-0.30) for the double-blind phase.

- The mean Z score change from baseline (at final visit) for height was slightly greater in pediatric patients 6-9 years old (- 0.20; N=38) for any topiramate dose compared to that in older pediatric patients 10-15 years (- 0.12, N=112) in open label, extensions studies.

- The mean Z score change from baseline (at final visit) for height was moderately greater in pediatric patients 6-9 years old (- 0.33; N=38) for any topiramate dose compared to that in older pediatric patients 10-15 years (- 0.18, N=102) in combined double-blind and open label study phases.

- The mean Z score change from baseline (at final visit) for height was smaller in pediatric patients 6-9 years old (- 0.52; N=36) for any topiramate dose compared to the change in older pediatric patients 10-15 years (- 0.80, N=102) in combined double-blind and open label study phases.

- The mean Z score change from baseline for BMI was similar and not greater in pediatric patients 6-9 years old (- 0.16; N=38) for any topiramate dose the change in older pediatric patients 10-15 years (- 0.23, N=104) in open label, extension studies.

- There were no clear consistent effects of serum bicarbonate (e.g., "low" or "not low") on Z score or Z score change from baseline for body weight, height/height velocity, or BMI.

Reviewer Comments

- With the exception of the height/linear growth data collected in the infant/toddler study, it is also important to recognize that height measurement in monotherapy and adjunctive treatment studies were not collected with appropriate attention to collecting high quality data as is ordinarily done when specific attention is directed toward collecting height data. For example, when specific attention is directed toward collecting high quality height/growth data, the protocol outlines specific procedures for collecting height such as everyone using the same measurement method (e.g., stadiometer) and collecting several measurements to obtain an average measurement for each visit and guidelines when data should not be retained and additional measurements should be collected.

- These height data which are not high quality data and which were collected primarily under open-label conditions over the long-term suggest that topiramate may decrease height. A warning for this possible adverse reaction is currently contained in the topiramate label because of the possibility of topiramate-induced metabolic acidosis decreasing growth and potentially, maximal height to be achieved. However, this warning is theoretical and not based upon actual prospectively collected data that were collected in an appropriate manner. Because it is important to know whether topiramate actually does decrease linear growth and cause growth retarding/delay, a prospective, randomized, double-blind, comparator-controlled study in pediatric patients for topiramate as monotherapy in pediatric patients (2-15 years) should be conducted and the requirement for such as study will be a Post-Marketing Requirement (PMR) for this NDA.

Adjunctive Therapy

- The treatment difference (Topiramate – Placebo) for Z score change from baseline (at final visit) for body weight was somewhat greater for pediatric patients 2-9 years (-0.23) than that for older pediatric patients 10-15 year (- 0.14) in the pooled, double-blind studies.

- There were no noteworthy treatment differences amongst the various pediatric age subgroups (2-5, 6-9, 2-9, 10-15 years) for Z score change from baseline (at final visit) for height for any topiramate dose in the open-label, extension studies.

- In the combined analyses of double-blind and open-label treatment phases, the Z score change from baseline for height for any topiramate dose was slightly greater in younger pediatric patients 2-9 years (-0.24, N= 196) than the change in older pediatric patients 10-15 years (-0.18, N = 124). Within the 2-9 year old group, the change in the 2-5 year old subgroup (- 0.32, N=86) appeared to be substantially greater than the change in the 6-9 year old subgroup (- 0.17, N = 110).

- The Z score change from baseline for BMI for any topiramate dose was fairly similar for young pediatric patients 2-9 years (-0.50, N = 291) and for older pediatric patients 10-15 years (- 0.45, N = 173). Within the 2-9 year old group, the change in the 2-5 year old subgroup (- 0.60, N=134) appeared to be substantially greater than the change in the 6-9 year old subgroup (- 0.41, N = 157).

- In the combined analyses of double-blind and open-label treatment phases, the Z score change from baseline for BMI for any topiramate dose was slightly greater in younger pediatric patients 2-9 years (-0.54, N= 196) than the change in older pediatric patients 10-15 years (-0.49, N = 124). Within the 2-9 year old group, the change in the 2-5 year old subgroup (- 0.68, N=86) appeared to be substantially greater than the change in the 6-9 year old subgroup (- 0.42, N = 110).

Reviewer Comment

- These open-label, long term data did not clearly suggest an effect of topiramate on decreasing height/linear growth. However, they were not analyzed in a manner to assess if there might be a dose-response with higher doses causing growth delay.

- The current topiramate label note in the pediatric section that infants/toddler treated up to 1 year with adjunctive topiramate during open-label study experienced significant/notable decreases in Z score change from baseline for height. However, because these data were uncontrolled and a significant proportion of these patients had associated neurological or systemic disorders, it is not possible to ascertain whether the decreases in linear growth were related to topiramate and/or the associated disorder. A prospectively planned, randomized, double-blind, comparator-controlled study of topiramate monotherapy in which pediatric patients (2-15 years) are treated up to 1 year and high quality height data are collected should answer this question and also inform if topiramate does cause this adverse reaction whether this adverse reaction appears to be related to the development of chronic metabolic acidosis.

7.4.4 Electrocardiograms (ECGs)

ECG data are analyzed only for double-blind studies. The following studies collected ECG measurements at baseline and double-blind endpoint: epilepsy adjunctive therapy studies Y1, Y2, Y3, YD, YE, YF, YG, YL, YP, and YTC/YTCE, and epilepsy monotherapy study TOPMAT-EPMN-104.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Not applicable

7.5.1 Dose Dependency for Adverse Events

TEAEs were analyzed for dose-dependent effects in section 7.4.1

7.5.2 Time Dependency for Adverse Events

Treatment-emergent adverse events (TEAEs) analyzed for time dependence as to whether they had their onset in the titration period, in the maintenance period, and whether they had their onset in the titration period and "persisted" into the maintenance period.

7.5.3 Drug-Demographic Interactions

Not applicable

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

Not applicable

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

Not applicable

7.6.3 Pediatrics and Assessment of Effects on Growth

See section 7.4.3 regarding height analyses in monotherapy and adjunctive therapy studies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

There were no new safety signals described for young pediatric patients $\leq$ 9 years old.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

Label recommendations are provided separately in a draft of the label.

9.3 Advisory Committee Meeting

Not applicable

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/s/

LEONARD P KAPCALA

07/15/2011

Norm, Here is my review for NDA 20505. I will also link my review to NDA 20844. Please let me know if any questioins. Thanx. Len

NORMAN HERSHKOWITZ

07/15/2011