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Pediatric and Maternal Health Staff Memorandum

Date: January 15, 2013

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To: Division of Neurology Products (DNP), CDER Office of Regulatory Policy, FDA Office of Chief Counsel

Drug: Trokendi XR (topiramate) extended-release capsules

NDA: 201635

Applicant: Supernus Pharmaceuticlas, Inc.

Subject: PMHS Response to Supernus Pharmaceutical Inc. October 31, 2012, Request for Comment Submission

INTRODUCTION AND BACKGROUND

Supernus requested a meeting with the Agency by letter dated July 24, 2012, to discuss the Tentative Approval action taken on June 25, 2012, for Trokendi XR (topiramate) extended-release capsules, NDA 201635. The Office of Chief Counsel (OCC), the Office of Regulatory Policy (ORP), the Division of Neurology Products (DNP), and the Pediatric and Maternal Health Staff (PMHS) met with the Applicant on October 3, 2012, to discuss the Tentative Approval action related to the Pediatric Exclusivity attached to Topamax[1] for the use of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, and the need for this information to appear in Trokendi XR labeling. The Applicant was told that they could submit for review, supported, alternative pediatric use language for the labeling of Trokendi XR and the Agency would determine if this information appropriately conveyed the pediatric safety information that is currently protected in Topamax labeling.[2]

On October 31, 2012, Supernus Pharmaceuticals Inc. submitted a Request for Comment (b) (4) pertaining to the Tentative Approval action taken on June 25, 2012, for Trokendi XR (topiramate) extended-release capsules, NDA 201635. Supernus submitted published literature to support the inclusion of alternative pediatric use information in the Trokendi labeling. OCC, ORP, DNP, and PMHS are reviewing the Applicant's October 31, 2012 Request for Comment Submission. Although PMHS's review summarizes some of the Agency's legal and policy discussions, PMHS's review will focus on the Applicant's clinical/scientific arguments for protected pediatric use labeling language alternatives. This review has also been prepared in consultation with DNP and other components of the Agency.

BACKGROUND

Best Pharmaceuticals for Children Act & Pediatric Research Equity Act

The goal of both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is to provide pediatric information in labeling to encourage the appropriate use of medications to treat pediatric patients. BPCA incentivizes Applicants to conduct pediatric studies by awarding an additional 6 months of exclusivity for voluntarily conducting FDA-requested studies under a Written Request (21 USC 355a). PREA requires certain applications to contain pediatric assessments under certain circumstances and authorized FDA to require holders of certain types of approved marketing applications to conduct pediatric studies under certain circumstances (21 USC 355c).

Labeling must be updated with the results of studies conducted under BPCA or PREA regardless of whether safety and effectiveness are established. In general, pediatric use information is incorporated solely in subsection 8.4 if safety and effectiveness are not

[1] Janssen Pharmaceuticals was awarded 3 years of Hatch-Waxman Exclusivity (expires December 22, 2012) for "information from pediatric studies added to the label" (M-54) , and an additional six months of Pediatric Exclusivity (expires June 22, 2013) under Best Pharmaceuticals for Children Act for meeting the terms of the Pediatric Written Request (PWR) (December 14, 2005)for Topamax® Tablets and Sprinkle Capsules.

[2] See October 3, 2012, meeting minutes.

established (with the exception of necessary contraindications and/or warnings and precautions) so as not to imply an indication. In contrast, pediatric use information is incorporated into all relevant sections of labeling when safety and effectiveness are established. FDA regulations include drug labeling provisions specific to the use of drugs in pediatric populations which are intended to maximize the availability of important pediatric safety information (e.g., 201.57(f)(9)).

Trokendi XR

On August 30, 2011, Supernus Pharmaceutical, Inc. submitted a 505(b)(2) New Drug Application for Trokendi XR (topiramate) extended-release capsules, NDA 201635. Supernus relies on the Agency's previous findings of safety and effectiveness for the listed drugs, Topamax tablets (NDA 20505) and capsules (NDA 20844). Supernus submitted only pharmacokinetic data to establish a bridge and bioequivalence from the approved immediate-release topiramate product to their extended-release topiramate product.

A Tentative Approval was issued on June 25, 2012, because FDA made the determination that the protected pediatric use information that appears in Topamax labeling related to the use of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months must remain in this Trokendi XR labeling for reasons of safe use Topamax Pediatric Exclusivity expires June 22, 2013).[3] Effectiveness was not demonstrated and an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality, were observed in the infant/toddler Topamax clinical study.[4]

Of note, FDA also had previously determined that this protected pediatric use information was necessary for the safe use of generic topiramate products and; therefore, this text was retained in generic topiramate labeling in accordance with the Best Pharmaceuticals for Children Act (BPCA).[5,6]

(b) (4)

The Pediatric Written Request was issued July 9, 2004 and amended December 14, 2005, requesting studies of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive.

[5] Section 505A(o) of the Best Pharmaceuticals for Children Act (BPCA) (section 505A(o) of the Food, Drug and Cosmetic Act) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. It provides that abbreviated new drug applications (ANDAs) may include protected warnings, precautions and contraindications and other information necessary to assure safe use regardless of whether such information is otherwise protected by exclusivity.

[6] See March 9, 2010, PMHS consult re: proposed labeling for generic topiramate tablets; See September 10, 2012, PMHS consult re: generic topiramate capsules and tablets. In September 2012, the Agency sent follow-up letters to applicants asking them to ensure the labeling was updated to include the information deemed necessary for safe use of the products.

Indications
Topamax is approved for the following indications:

- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS)
- Migraine: Treatment for adults for prophylaxis of migraine headache

Supernus received a Tentative Approval for the following indications for Trokendi XR:

- initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures;
- adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures;
- adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Reviewer Comment: Topamax is approved for initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures; however, the 2 to 10 year old age group is protected by 3 years of Waxman-Hatch Exclusivity – New Patient Population (expires July 14, 2014). This study information fulfilled the Pediatric Research and Equity Act (PREA) postmarketing studies requirement issued June 29, 2005. No unique safety concerns were identified in these studies, and FDA determined that protected pediatric information regarding this population was not necessary for the safe use of *Trokendi.*

Topamax Infant/Toddler Labeling[7]
The infant/toddler protected pediatric use information was incorporated in the following sections/subsections of Topamax labeling:[8]

5 WARNINGS AND PRECAUTIONS
- 5.4 Metabolic Acidosis
- 5.8 Hyperammonemia and Encephalopathy
- 5.9 Kidney Stones
- 5.13 Monitoring: Laboratory tests

8 USE IN SPECIFIC POPULATIONS
- 8.4 Pediatric Use

[7] See Appendix A for side by side comparison of approved Topamax Pediatric Use Labeling and proposed Supernus Pediatric Use Labeling
[8] See current approved Topamax labeling, dated October 29, 2012

Reviewer Comment: The WARNINGS, AND PRECAUTIONS subsections 5.4, 5.8, 5.9, and 5.13, existed in Topamax labeling prior to the addition of the infant/toddler study results. These WARNINGS AND PRECAUTIONS subsections were updated and revised with the additional data from the infant/toddler study.

Applicant Arguments

Supernus believes that a Full Approval should be granted for Trokendi XR and requests the Agency to reconsider its Tentative Approval decision based on the following arguments:

(b) (4)

Supernus provided proposed (b) (4)

(b) (4)

PMHS SUMMARY RESPONSES

1. (b) (4) of label language for a 505(b)(2) New Drug Application.

   The Applicant states that their product is not intended for use in children under 6 years of age which they assert is clearly stated in Trokendi XR labeling. Furthermore, the Applicant states that FDA's labeling regulations permit the Agency to require statements that are related to uses not listed in the Indications and Usage section in labeling only in specific circumstances (i.e., if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard). (b) (4)

PMHS Response

Pediatric product development legislation (BPCA and PREA) was enacted because of the recognition that drugs approved for adults for indications that occurred in pediatric populations were being used in pediatric populations despite the lack of adequate labeling for those populations, with potentially dangerous results. BPCA and PREA together used a "carrot and stick" approach to address the lack of pediatric information in drug labeling and to ensure drugs for indications that occur in children would be appropriately labeled for use in children. Prior to the enactment of pediatric legislation, there was a paucity of drugs that contained pediatric labeling to adequately inform use of a drug in children and the majority of drugs used in children were used without appropriate safety, effectiveness or dosing information for pediatric age groups. Outpatient utilization data presented at the Pediatric Advisory Committee Meeting on September 23, 2011, reported 8900 Topamax prescriptions in patients 0 to 1 year of age between April 2007 and March 2011.[9] There is no infant/toddler age group indication for Topamax and the Topamax study conducted in this age group failed to demonstrated effectiveness, but demonstrated an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality. However, there are few anti-epileptic drugs approved in infants and toddlers and topiramate is used for seizure control when necessary in this age group. Because of the efficacy and safety concern with the use of topiramate in infants and toddlers, clinicians need access to the available benefit/risk information for informed prescribing decisions. Further, labeling regulations (e.g., 21 CFR 201.57(f)(9)) require labeling to include a description of hazards associated with use of a drug in a pediatric population for which the requirements for substantial evidence of effectiveness have not been met. (b) (4) .

2. The information that the Division requests (b) (4)

   The Applicant states that their extended-release topiramate product is not intended for use in infants and toddlers and that they have placed appropriate messages in labeling regarding the need to swallow the capsule whole and not open and sprinkle on food, or chew or crush. The Applicant also states that safety and efficacy were not established in the Topamax study conducted in pediatric patients ages 1 to 24 months; (b) (4)

PMHS Response

FDA, not the Applicant, makes the determination (b) (4) is necessary to ensure the safe use of both 505(j) and 505(b)(2) products. (b) (4) (b) (4)

[9] See Pediatric Safety Review - Topamax, Pediatric Advisory Committee Meeting, September 23, 2011

In addition, there is no evidence to suggest, despite labeled warnings, that the Trokendi XR capsule will not be opened. The capsule can be opened and is likely to be opened for use in a patient of any age who is unable to swallow capsules whole.

As previously noted, there are few anti-epileptic drugs approved for infants and toddlers. The fact that effectiveness with Topamax was not established in young patients; and an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality, were observed, make it is all the more compelling to include this information in all topiramate labeling. The assignment of safety effects in the absence of effectiveness is important to provide benefit/risk information for prescribing decisions in children. For this very reason, drug product labeling is required to be updated with the results of studies conducted under BPCA or PREA regardless of whether safety and effectiveness were established. (b) (4)

(b) (4)

PMHS Response

A 505(b)(2) drug product is not required to have labeling that is identical to the listed drug. Supernus submitted a 505(b)(2) application which relies on the Agency's findings of safety and efficacy for Topamax, and submitted only pharmacokinetic data to establish a bridge and bioequivalence from the approved immediate-release topiramate product to their extended-release topiramate product. In addition, the Applicant itself proposed identical labeling to Topamax for the sections of labeling that they relied on for previous findings of safety and efficacy, including the protected infant/toddler study information.

(b) (4)

Regardless, FDA has determined that the information on the infant/toddler study is necessary for the safe use of Trokendi XR.

Reviewer Comment: Supernus did not include the Topamax adult migraine indication in Trokendi XR labeling, as the migraine indication remains under patent protection.

During the June 29, 2012, teleconference, FDA told the Applicant that section 505A(o) of the FD&C Act (BPCA) allows the retention of protected pediatric use information in 505j products when the protected pediatric use information is necessary for the safe use of the generic drug product. The Agency previously determined that the infant/toddler information is necessary for the safe use of topiramate generic products. There are no provisions allowing retention of protected but essential pediatric information for 505(b)(2) products. When FDA determines that protected pediatric use information must remain in a 505(b)(2) product's labeling for reasons of safe use, then the Applicant can receive only a Tentative Approval until the exclusivity expires.

4. (b) (4)

PMHS Response

The Applicant's contention that the public health is promoted with once daily topiramate versus twice daily topiramate because one daily dosing increases patient compliance is speculative. The Applicant did not study patient compliance of these different dosing regimens, or the effect of these different dosing regimens on seizure control. Furthermore, although not studied, missing a dose of a once daily topiramate product versus missing one dose of a twice-a-day immediate release topiramate product may have a worse adverse impact on seizure control.

The Applicant did not provided sufficient data to FDA to support their claim that a (b) (4) Furthermore, as previously stated, the information from the Topamax infant/toddler study should appear in all topiramate labeling for benefit/risk prescribing decisions when topiramate is considered as an option for use in young children with seizure disorders, as effectiveness was not established and safety concerns were observed. Therefore, PMHS disagrees with the Applicant's argument that the (b) (4)

Proposed Pediatric Use Labeling[10]

The Applicant proposed (b) (4) for Trokendi XR labeling in (b) (4) .

PMHS Response

A detailed description of the infant/toddler study appears in the Pediatric Use subsection of Topamax labeling, with important data from the study further described in various subsections of the Warnings and Precautions section of labeling. The Applicant's proposed (b) (4) For example, the Applicant's proposed (b) (4) Appendix A includes a side by side comparison of the Topamax labeling and Trokendi XR proposed labeling, and explains why the Trokendi proposed labeling is not adequate. The Trokendi XR pediatric use language (b) (4) .

CONCLUSIONS Supernus failed to provide an adequate justification to support the (b) (4) (b) (4) labeling; pediatric use information that is protected by Pediatric Exclusivity until June 22, 2013. FDA determined that this protected pediatric use information was necessary for the safe use of Trokendi XR. No topiramate product is approved in the infant/toddler age group. The Topamax study conducted in this vulnerable population failed to demonstrate efficacy, but an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality, were observed. There are few anti-epileptic drugs approved in infants and toddlers and drugs approved for adults or older pediatric patients are likely to be used in this population. Clinicians require adequate risk/benefit information, when available in drug product labeling, for making prescribing decisions when considering use in an infant or toddler. The Applicant failed (b) (4) .

RECOMMENDATIONS

PMHS recommends that the Applicant be informed that they failed to provide an adequate justification to support (b) (4) In addition, the Applicant failed to (b) (4)

[10] See Appendix A for side by side comparison of approved Topamax Pediatric Use Labeling and proposed Supernus Pediatric Use Labeling


(b) (4)

APPENDIX A – Side-By-Side Pediatric Use Labeling

Protected Topamax Pediatric Use Labeling (Infant/Toddler Study)	Proposed Alternative Topiramate Extended-Release Capsules Pediatric Use Labeling	PMHS Comments
5.4 Metabolic Acidosis Although not approved for use in patients under 2 years of age with partial onset seizures, a controlled trial that examined this population revealed that topiramate produced a metabolic acidosis that is notably greater in magnitude than that observed in controlled trials in older children and adults The mean treatment difference (25 mg/kg/d topiramate-placebo) was -5.9 mEq/L for bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate < 20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/d, 50% for 15 mg/kg/d, and 45% for 25 mg/kg/d [*see Pediatric Use (8.4)*]. Long-term, open-label treatment of infants/toddlers, with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in Z SCORES for length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal infants. Reductions in Z SCORES for length and weight were correlated to the degree of acidosis *[see Pediatric Use (8.4)]*. **5.8 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)** …and in very young pediatric patients (1-24 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10 % for 5 mg/kg/day, 0 % for 15 mg/kg/day, 9 % for 25 mg/kg/day). Topiramate is not approved as monotherapy for migraine	(b) (4)	The Applicant's proposed (b) (4) .

prophylaxis in adolescent patients or as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. Although topiramate is not indicated for use in infants/toddlers (1-24 months) VPA clearly produced a dose-related increased in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8 % for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term, extension trial in these very young, pediatric patients *[see Use in Specific Populations (8.4)]*.	(b) (4)	
5.9 Kidney Stones During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones that were diagnosed clinically or by sonogram. Topiramate is not approved for pediatric patients less than 2 years old *[see Pediatric Use (8.4)]*.	**5.9 Kidney Stones** No alternate language proposed by Applicant.	(b) (4)
5.13 Monitoring: Laboratory Tests Changes in several clinical laboratory values (increased creatinine, BUN, alkaline phosphatase, total protein, total eosinophil count and decreased potassium) have been observed in a clinical investigational program in very young (<2 years) pediatric patients who were treated with adjunctive topiramate for partial onset seizures [*see Pediatric Use (8.4)*].	(b) (4)	(b) (4)

(b) (4)

(b) (4)

(b) (4)

8.4 Pediatric Use

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 study, 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 *[see Adverse Reactions (6)]*.

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 noteworthy increased incidence (topiramate 25 mg/kg/day 5%, placebo 0%) of a markedly abnormal increase [see Warnings

(b) (4)

and precautions (5.15)]. 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 (5.15)]*. 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 *[see Warnings and Precautions (5.9)]*. Treatment with topiramate for up to 1 year was associated with reductions in Z SCORES for length, weight, and head circumference *[see Warnings and Precautions (5.3) and Adverse Reactions (6)]*. In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment-related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) *[see Warnings and Precautions (5.5)]*.	(b) (4)	

In this open-label, uncontrolled study, the mortality was 37 deaths/1000 patient years. It is not possible to know whether this mortality rate is related to topiramate treatment, because the background mortality rate for a similar, significantly refractory, young pediatric population (1-24 months) with partial epilepsy is not known.		

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/s/

JEANINE A BEST
01/15/2013

HARI C SACHS
01/15/2013
I agree with these recommendations.

LYNNE P YAO
01/15/2013

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Pediatric and Maternal Health Staff Memorandum

Date: June 12, 2012

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Lisa Mathis, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP)

Drug: Trokendi (topiramate) extended-release capsules

NDA: 201635

Sponsor: Supernus Pharmaceuticlas, Inc.

Subject: 505(b)(2) Application and protected pediatric information (Pediatric and Waxman-Hatch Exclusivity)

INTRODUCTION AND BACKGROUND

On August 30, 2011, Supernus Pharmaceutical, Inc. submitted a 505(b)(2) New Drug Application for Trokendi (topiramate) extended-release capsules, NDA 201635. The Reference Listed Drug (RLD) is Topamax (topiramate) tablets for oral use, NDA 20505. Supernus is relying on findings of safety and efficacy from NDA 20505 and has submitted only pharmacokinetic data to establish a bridge and bioequivalence from the approved immediate-release topiramate product to their extended-release topiramate product.

Topamax is approved for the following indications:

- *Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures*
- *Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS)*
- *Migraine: Treatment for adults for prophylaxis of migraine headache*

Supernus is seeking approval for the following indications for Trokendi:

- *Monotherapy epilepsy: Initial monotherapy in patients* (b) (4) *with partial onset or primary generalized tonic-clonic seizures.*
- *Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients* (b) (4) *with partial onset seizures or primary generalized tonic-clonic seizures, and in patients* (b) (4) *with seizures associated with Lennox-Gastaut syndrome (LGS).*

Janssen Pharmaceuticals was awarded 3 years of Waxman-Hatch Exclusivity (expires December 22, 2012) for revisions to Topamax labeling based on data submitted in response to a Pediatric Written Request (December 14, 2005), and an additional six months of Pediatric Exclusivity (expires June 22, 2013) under BPCA for meeting the terms of the PWR for Topamax® Tablets and Sprinkle Capsules, and the company was awarded three-years of Waxman-Hatch (W-H) Exclusivity. The Pediatric Written Request was issued July 9, 2004 and amended December 14, 2005, requesting studies of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive. Efficacy was not demonstrated and an increased risk of known drug-related adverse reactions as well as unique safety concerns, including death, were observed in pediatric studies with Topamax for use as adjunctive therapy in the treatment of partial seizures in patients 1 month to 24 months of age. The study data was incorporated in the Pediatric Use subsection of Topamax labeling and retained in generic topiramate labeling for reasons of safe use, as allowed by the Best Pharmaceuticals for Children Act (BPCA).[1] BPCA does not have carve-out or

[1] The Best Pharmaceuticals for Children Act (BPCA) (section 505A of the Food, Drug and Cosmetic Act) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling.

retention provisions for protected pediatric information in 505(b)(2) products. both PMHS and DNP agreed that this protected pediatric use information must remain in Trokendi labeling for reasons of safe use; therefore, Trokendi cannot receive a full approval until expiration of the Pediatric Exclusivity on June 22, 2013. A Tentative Approval may be issued in the interim.

Janssen Pharmaceuticals was awarded 3 years of Waxman-Hatch Exclusivity – New Patient Population (expires July 14, 2014) for revisions to Topamax labeling to include pediatric use information for initial monotherapy in patients 2 to 10 years of age with partial onset or primary generalized tonic-clonic seizures. This study information fulfilled the Pediatric Research and Equity Act (PREA) postmarketing commitment issued June 29, 2005. The data submitted for the approval of monotherapy in this age group was a re-analysis of previous submitted data in or determine appropriate monotherappy dosing in pediatric patients ages 2 to 10 years of age. Generic topiramate labeling does not contain this protected pediatric use information as generic topiramate was approved prior to the monotherapy approval in pediatric patients 2 to 10 years of age. No unique safety concerns were noted in the previously submitted efficacy trials for initial monotherapy in patients 2 to 10 years of age with partial onset or primary generalized tonic-clonic seizures. This protected pediatric safety information may be safely omitted from Trokendi labeling.

PMHS RECOMMENDATIONS

1. The protected pediatric use information related to the use of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months must remain in Trokendi labeling for reasons of safe use; therefore, Trokendi cannot receive a full approval until expiration of the Pediatric Exclusivity on June 22, 2013.

2. The protected pediatric use information related to initial monotherapy in pediatric patients 2 to 10 years of age with partial onset or primary generalized tonic-clonic seizures may be safely omitted from Trokendi labeling; therefore the approval of Trokendi is not impacted by the Waxman-Hatch New Patient Population Exclusivity that expires on July 14, 2014.