ORTHO-McNEIL NEUROLOGICS, INC.

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ALERT: TOPAMAX® (topiramate) AND TOPROL-XL® (metoprolol succinate) MEDICATION ERRORS

September 2005

Dear Healthcare Professional:

Ortho-McNeil Neurologics, Inc. has become aware of reports of medication errors involving TOPAMAX® (topiramate) tablets and TOPROL-XL® (metoprolol succinate) extended-release tablets, a product of AstraZeneca LP, leading to patient exposure to the wrong drug.

Based on a review of spontaneous reports submitted to the Food and Drug Administration, World Health Organization, and the United States Pharmacopoeia, prescriptions for TOPAMAX® and TOPROL-XL® have been incorrectly written, interpreted, labeled, and/or dispensed. Possible explanations for these medication errors include similarity in names between TOPAMAX® and TOPROL-XL®, proximity of the two products on pharmacy shelves and/or in computerized listings, and identical dose strengths in the tablet formulations.

Efforts to address this situation are currently under way within pharmacies, as part of a broad range of activities the company is undertaking to raise awareness of the issue in the pharmacy and medical communities and with patients taking TOPAMAX®.

TOPAMAX® and TOPROL-XL® are available in identical strengths but can be distinguished by their shapes, color and markings (see Figures 1 and 2). Another similarity between TOPAMAX® and TOPROL-XL® is dose titration, which is recommended for both products when initiating therapy. The TOPAMAX® starting dose may be administered once or twice daily, maintenance dosing is twice daily; and the TOPROL-XL® starting and maintenance dosing is once daily.

Figure 1: TOPAMAX® (topiramate) Tablets are available as debossed, coated and round tablets.

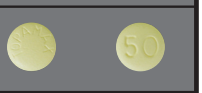
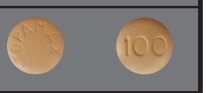
Tablet	Color	Engraving	Sample
25 mg	White	"TOP" on one side, "25" on the other	
50 mg	Light-Yellow	"TOPAMAX" on one side, "50" on the other	
100 mg	Yellow	"TOPAMAX" on one side, "100" on the other	
200 mg	Salmon	"TOPAMAX" on one side, "200" on the other	

Figure 2: TOPROL-XL® (metoprolol succinate) extended release tablets are available as white, biconvex, film-coated and scored tablets.

Tablet	Shape	Engraving	Sample
25 mg*	Oval	A ß	
50 mg	Round	A mo	
100 mg	Round	A ms	
200 mg	Oval	A my	

*The 25 mg tablet is scored on both sides.

TOPAMAX® is indicated for the treatment of epilepsy and migraine prevention. Antiepileptic drugs, including TOPAMAX®, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency in patients with or without a history of seizures or epilepsy.

TOPROL-XL® is indicated for the treatment of hypertension, long-term treatment of angina pectoris, and heart failure NYHA Class II or III. TOPROL-XL® has a boxed warning against abrupt cessation of therapy.

Patients who receive incorrect medications are at risk of experiencing potentially serious health consequences associated with unintended exposure or the lack of a needed therapy.

WHAT YOU CAN DO TO REDUCE THE POTENTIAL FOR MEDICATION ERRORS

- Be alert to the possibility of medication errors
- Write full and legible prescriptions for these products and communicate oral prescriptions clearly
- Use both brand and generic names when communicating drug names
- Discuss the indications and proper use of these medications with patients
- Alert patients that they should carefully check the medication they receive and promptly bring any questions or concerns to the attention of their pharmacist

INDICATIONS for TOPAMAX®

Monotherapy Epilepsy- TOPAMAX®[1] is indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures. Effectiveness was demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials.

Adjunctive Therapy Epilepsy- TOPAMAX® is indicated as adjunctive therapy for adults and pediatric patients ages 2 – 16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Migraine- TOPAMAX® is indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

IMPORTANT SAFETY INFORMATION FOR TOPAMAX®

TOPAMAX® has been associated with serious adverse events including: hyperchloremic, non-anion gap metabolic acidosis (lowering of serum bicarbonate levels)—measurement of baseline and periodic serum

bicarbonate levels is recommended; acute myopia and secondary angle closure glaucoma—patients should seek medical attention if they experience blurred vision or ocular pain; oligohidrosis and hyperthermia—occurs most often in hot weather and in children; cognitive/psychiatric side effects, including somnolence and fatigue, cognitive dysfunction, and psychiatric/behavioral disturbances; hyperammonemia with or without encephalopathy—associated with the concomitant use of valproic acid; and kidney stones—patients should maintain an adequate fluid intake to minimize the risk of renal stone formation.

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

As monotherapy, the most common side effects of TOPAMAX® (in the 400 mg/day group and at a rate higher than the 50 mg/day group) in adults were: paresthesia, weight decrease, somnolence, anorexia, dizziness, and difficulty with memory; and in children: weight decrease, upper respiratory tract infection, paresthesia, anorexia, diarrhea, and mood problems.

Migraine
Most common adverse events associated with TOPAMAX® 100 mg vs placebo were paresthesia, anorexia, fatigue, nausea, diarrhea, weight decrease, and taste alteration.

INDICATIONS for TOPROL-XL®
TOPROL-XL®[2] is indicated for the treatment of hypertension, long-term treatment of angina pectoris, and heart failure NYHA Class II or III.

IMPORTANT SAFETY INFORMATION FOR TOPROL-XL®
TOPROL-XL® has a boxed warning against abrupt cessation of therapy.

If you become aware of any medication errors involving TOPAMAX®, report them immediately to us at 1-800-682-6532, and if TOPROL-XL® is involved, also report the error to AstraZeneca at 1-800-236-9933. Medication errors should also be reported to the USP Medication Error Reporting Program in cooperation with the Institute for Safe Medication Practices (1-800-23ERROR; 1-800-FAIL-SAF) or FDA's MedWatch Adverse Event Reporting Program (1-800-FDA-1088).

Thank you for your attention to this matter. For additional medical information about TOPAMAX®, please call 1-800-682-6532 from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Joseph Hulihan, M.D.
Vice President, Medical Affairs
Ortho-McNeil Neurologics, Inc.

PLEASE CONSULT ENCLOSED COMPLETE PRESCRIBING INFORMATION FOR TOPAMAX®[1].

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1. Package Insert – TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules. Ortho-McNeil Neurologics, Inc. Titusville, NJ 08560. REVISED JUNE 2005.

2. Package Insert – TOPROL-XL® (metoprolol succinate) Extended-Release Tablets. AstraZeneca LP. Wilmington, DE 19850. REVISED 2/05.