JANSSEN-ORTHO

IMPORTANT DRUG SAFETY INFORMATION

January 12, 2004

SUBJECT: TOPAMAX* (topiramate) use is associated with Metabolic Acidosis

Dear Healthcare Professional:

Janssen-Ortho Inc., following discussions with Health Canada, would like to inform you of emerging important safety information which indicates that TOPAMAX (topiramate) tablets and sprinkle capsules cause hyperchloremic, non-anion gap metabolic acidosis (decreased serum bicarbonate). TOPAMAX is approved and marketed as adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy who are not satisfactorily controlled with conventional therapy.

Data on hyperchloremic, non-anion gap metabolic acidosis are derived from placebo-controlled trials and post-marketing experience in over 2.5 million patients. In clinical trials, the rate of occurrence of a persistently decreased serum bicarbonate ranges from 23-67% for patients treated with topiramate and 1-10% for placebo. The incidence of markedly low serum bicarbonate in clinical trials ranges from 3-11% for topiramate and 0 to <1% for placebo.

Generally, decreases in serum bicarbonate occur soon after initiation of topiramate, although they can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate, with an average decrease of 4 mEq/L at daily doses of 400 mg in adults and approximately 6 mg/kg/day in pediatric patients. Rarely, patients can experience decrements to values below 10 mEq/L.

Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

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

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

Data related to Metabolic Acidosis

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

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

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

Although not approved for the prophylaxis of migraine, the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value < 17 mEq/L and > 5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and < 1% for placebo.

Safety and effectiveness in patients below the age of 2 years have not been established. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia (rickets) and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Topiramate overdose has resulted in severe metabolic acidosis.

Janssen-Ortho Inc. is currently working with Health Canada to update the Canadian labeling.

Janssen-Ortho Inc. continues to work closely with Health Canada to monitor ongoing clinical trials, and worldwide pharmacovigilance reports. Janssen-Ortho Inc. will continue to provide you with the most current and complete product information available for the management of patients receiving TOPAMAX.

The current Prescribing Information is available on the Janssen-Ortho Inc. website at www.janssen-ortho.com. Updates to the Prescribing Information will be posted on this website and will be provided for the next edition of *The Compendium of Pharmaceuticals and Specialties.*

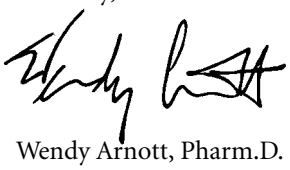
The identification, characterization and management of drug-related adverse events are dependent on the active participation of Healthcare Professionals in adverse event reporting programs. Healthcare Professionals are asked to report any suspected adverse events in patients receiving TOPAMAX (topiramate) to Janssen-Ortho Inc. at the following address:

Janssen-Ortho Inc.
Drug Safety and Surveillance
19 Green Belt Drive
Toronto, ON M3C 1L9 or call toll free at 1-800-567-3331 or email to dsscan@joica.jnj.com

Your professional commitment in this matter has an important role in protecting the well-being of your patients by contributing to early signal detection and informed use of drugs.

Should you have any questions or require additional information regarding the use of TOPAMAX (topiramate), please contact Janssen-Ortho Inc. Medical Information Department at 1-800-567-3331 from 9:00 a.m. to 5:00 p.m., Monday through Friday, EST.

Sincerely,



Wendy Arnott, Pharm.D.
Vice-President
Regulatory, Quality and Safety

Any suspected adverse drug reactions in patients receiving TOPAMAX* (topiramate) can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: 613-957-0337 or Fax: 613-957-0335
Toll free for consumers and health professionals:
Tel: 866-234-2345 or Fax: 866-678-6789
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceuticals and Specialties,* or on the TPD website, along with the ADR Guidelines at:

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adr_guideline_e.pdf

