METABOLIC ACIDOSIS ASSOCIATED WITH ZONEGRAN

This New Drug FAX Sheet issue provides information from the FDA regarding metabolic acidosis caused by Zonegran (zonisamide). The verbatim communication from the FDA and prescribing recommendations are provided below. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.

Zonisamide is an antiepileptic drug that is approved as adjunctive therapy for the treatment of partial seizures in adults with epilepsy. Following a review of updated clinical data, the FDA has determined that treatment with zonisamide can cause metabolic acidosis in some patients.

The development of metabolic acidosis generally appears to be dose-dependent and can occur at doses as low as 25 mg daily. The zonisamide-related decreases in serum bicarbonate are usually mild to-moderate (average decrease of about 2 mEq/L) in adult patients treated with various doses of zonisamide. However, some adult patients have experienced severe serum bicarbonate decreases as much as 10 mEq/L below their baseline. Conditions or therapies that predispose patients to developing acidosis (such as renal disease, severe respiratory disorders, diarrhea, surgery, ketogenic diet, or other medications) may worsen the bicarbonate-lowering effects of zonisamide.

The pivotal, placebo-controlled trials supporting the approval of zonisamide as adjunctive epilepsy treatment in adults did not collect serum bicarbonate data.

Zonisamide is not approved for the treatment of epilepsy in pediatric patients, as monotherapy treatment of epilepsy in adults, or for migraine prophylaxis in adults. However, serum bicarbonate data have been collected in various clinical development programs for these off-label indications. These data show that zonisamide treatment can cause metabolic acidosis in these patients.

The pediatric program consisted primarily of a large open-label, uncontrolled, adjunctive treatment trial of patients aged 3-16 years with partial epilepsy. In that trial, the incidence of a persistent decrease in serum bicarbonate to levels less than 20 mEq/L was up to 90% and generally increased with higher doses. The incidence of a persistent markedly abnormally low serum bicarbonate value (less than 17 mEq/L and more than 5 mEq/L decrease from a pretreatment value of at least 20 mEq/L) was as high as 18% and appeared to increase with higher doses.

In placebo-controlled studies of zonisamide monotherapy in adults with epilepsy or as prophylaxis for migraine in adults, the incidence of a persistent treatment-emergent decrease in serum bicarbonate (to <20 mEq/L) ranged from 21% in patients treated with a 25 mg daily dose to 43% in patients treated with a 300 mg daily dose. The incidence of persistent abnormally low serum bicarbonate was 2% or less across all doses evaluated.

The relatively high frequencies of varying severities of metabolic acidosis observed in pediatric patients (compared to the frequency and severity of metabolic acidosis observed in adults) suggest that pediatric patients may be more at risk than adults to developing metabolic acidosis.

The FDA urges both healthcare professionals and patients to report side effects from the use of zonisamide (marketed as Zonegran) and its generics to the FDA’s MedWatch Adverse Event Reporting program available:

- online at www.fda.gov/medwatch/report.htm
- by returning the postage-paid FDA form 3500 available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787
- faxing the form to 1-800-FDA-0178
- by phone at 1-800-332-1088

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Recommendations and Information for Healthcare Providers to consider when prescribing zonisamide (marketed as Zonegran) and generics:

- Zonisamide can cause metabolic acidosis, characterized by hyperchloremia and decreased serum bicarbonate. Metabolic acidosis is often asymptomatic.

- Generally, zonisamide-induced metabolic acidosis occurs early in treatment, but may occur at any time during treatment.

- The risk of development of zonisamide-induced metabolic acidosis appears to be greater at higher doses of zonisamide, but can occur with doses as low as 25 mg daily.

- Conditions or therapies that may predispose patients to acidosis include renal disease, severe respiratory disorders, diarrhea, surgery, ketogenic diet, or other drugs (e.g. acetazolamide)

- Younger patients may be at risk for zonisamide-induced metabolic acidosis. Data from one pediatric clinical trial shows a higher incidence of metabolic acidosis compared to data from trials of zonisamide in adults.

- Signs and symptoms of persistent metabolic acidosis may include hyperventilation, fatigue and anorexia. More severe symptoms may include cardiac arrhythmias and stupor.

- Chronic, untreated metabolic acidosis may increase the risk for kidney stones, nephrocalcinosis, and bone abnormalities (e.g., osteoporosis, osteomalacia, and rickets in pediatric patients) with an increased risk for fractures.

- Chronic metabolic acidosis in pediatric patients can reduce growth rates, resulting in a reduction in the maximal height achieved. The specific effects of zonisamide on growth and bone have not been investigated.

- Although the effects of metabolic acidosis from zonisamide on the fetus are not clearly known, metabolic acidosis in pregnancy (due to other causes) may affect fetal development (i.e., decreased fetal growth, decreased fetal oxygenation and fetal death) and the ability of the fetus to tolerate labor. In addition, significant amounts of zonisamide can appear in the breast milk of nursing women taking zonisamide, and the effects of this exposure on the infant from metabolic acidosis, or any other cause, are unknown.

- A pre-treatment (baseline) and periodic measurements of serum bicarbonate are recommended during zonisamide treatment. In addition, if signs or symptoms of metabolic acidosis are observed, serum bicarbonate should be measured.

- If metabolic acidosis develops and persists, consideration should be given to reducing the dose of zonisamide, or to discontinuing zonisamide using dose tapering and modifying the patient’s treatment as appropriate. If the decision is made to continue patients with persistent acidosis on zonisamide, then alkali treatment should be considered.

Prepared by: Terri M. Wensel, Pharm.D.