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## IMPORTANT DRUG WARNING

Dear Healthcare Professional:

We have updated the prescribing information for ZONEGRAN® (zonisamide) to provide new information about oligohidrosis and hyperthermia in pediatric patients. This event is characterized by decreased sweating and an elevation in body temperature above normal. This information is based on about 350,000 patient-years of exposure in pediatric patients.

As of December 31, 2001, there have been 40 reported cases: 38 in the first 11 years of marketing in Japan, and 2 in the first year of marketing in the US. It is generally recognized that postmarketing data are subject to under-reporting. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases. There have been no reported deaths.

Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with Zonegran should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather.

The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.

The following bolded WARNING has been added to the ZONEGRAN prescribing information:

### **Oligohidrosis and Hyperthermia in Pediatric Patients**

**Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.**

**During the pre-approval development program in Japan, one case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases were reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.**

**In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case per 10,000 patient-years of exposure. In the first year of marketing in the US, 2 cases were reported, an estimated reporting rate of about 12 cases per 10,000 patient-years of exposure. These rates are underestimates of the true incidence because**



**of under-reporting. There has been one report of heat stroke in an 18 year-old patient in the US.**

**Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases. There have been no reported deaths.**

**Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with Zonegran should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when zonisamide is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, carbonic anhydrase inhibitors and drugs with anticholinergic activity.**

**The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.**

You can further our understanding of adverse events by reporting all cases to Elan at the contact number below or to the FDA MedWatch Program by phone 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail (using postage-paid form) MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or via [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

A copy of the full Prescribing Information is enclosed for your reference. If you have any questions regarding ZONEGRAN capsules, please feel free to call Elan Medical Information Services at 1-888-NEURO-05 (1-888-638-7605).

Sincerely,

A handwritten signature in black ink, appearing to read "CFO'Brien", with a long horizontal flourish extending to the right.

Chris O'Brien, MD  
Vice President, Medical Affairs

Enclosure: Zonegran® (zonisamide) capsules Package Insert