ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
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Abbott Park, IL 60064-6182

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IMPORTANT DRUG WARNING

Dear Health Care Professional:

In patients with known or suspected urea cycle disorders (UCD), a group of uncommon genetic abnormalities, there have been reports of hyperammonemic encephalopathy, including fatalities, with valproate therapy. This information has been added to the package inserts for Depakote® Tablets (divalproex sodium delayed-release tablets, Abbott Laboratories),[1] Depakote® ER Tablets (divalproex sodium extended-release tablets, Abbott Laboratories), Depakote® Sprinkle Capsules (divalproex sodium coated particles in capsules, Abbott Laboratories), Depakene® Capsules and Syrup (valproic acid capsules and syrup, Abbott Laboratories), and Depacon® (valproate sodium injection, Abbott Laboratories).

The overall prevalence of UCD is considered to range from 1:8,000 births[2] to 1:30,000 births[3]. Patients with UCD have an impaired ability to produce urea, a nontoxic elimination end-product of ammonia metabolism. A genetic defect or deficiency in one of the enzymes of the urea cycle causes the UCD. Patients with UCD may exhibit clinical signs and symptoms of hyperammonemia, encephalopathy, and respiratory alkalosis, with onset occurring either during the neonatal period or later in life (ranging from infancy to adulthood). Diagnostic evaluation for UCD may include measurement of blood gases and the plasma ammonia level, quantitative analysis of plasma amino acids and urine orotate, and qualitative analysis of urine for organic acids by gas chromatography and mass spectroscopy.[2]

The following changes to the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections have been made to the product label:

CONTRAINDICATIONS
Divalproex sodium is contraindicated in patients with known urea cycle disorders (see **WARNINGS**).

WARNINGS
Urea Cycle Disorders (UCD)
Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: (1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; (2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; (3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); (4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (see **PRECAUTIONS**).

PRECAUTIONS
Hyperammonemia
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see **WARNINGS – Urea Cycle Disorders**).

Asymptomatic elevations of ammonia are more common and, when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

Changes consistent with the revised labeling have also been made to the Information for Patients subsection of the PRECAUTIONS section and to the ADVERSE REACTIONS section of the label. A copy of the revised Depakote® Tablets package insert is enclosed. Identical revisions have been made to the product labels for all of our valproate products.

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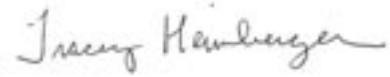
As with all medical products, health care professionals are strongly encouraged to report any serious adverse events that occur with the use of Depakote®, Depakote® ER, Depacon® or Depakene® products, either to Abbott Laboratories by phone (1-800-633-9110), or to the FDA's MedWatch program. The MedWatch form may be submitted online (www.fda.gov/medwatch), by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by mail (using postage-paid form) to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787.

If you have any questions regarding a Depakote® product, our Medical Information Department may be contacted by phone at 1-800-633-9110.

Sincerely,



Tracey Heimberger, MD
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References:

1. Depakote® Tablets Package Insert. Abbott Park, Ill: Abbott Laboratories.
2. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. In: Barness LA, DeVivo DC, Kaback MM, Morrow G, Oski FA, Rudolph AM, eds. *Advances in Pediatrics.* Chicago, Ill: Mosby; 1996:127-170.
3. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J Pediatr.* Jan 2001;138(suppl 1):S6-S10.

Enclosure:

Depakote® Tablets Package Insert. Abbott Park, Ill: Abbott Laboratories.