



U.S. Food and Drug Administration  
Protecting and Promoting Your Health

## Drug Safety Communications

### **FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children**

#### **Safety Announcement**

**[05-06-2013]** The U.S. Food and Drug Administration (FDA) is advising health care professionals and women that the anti-seizure medication valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. Based on information from a recent study, there is evidence that these medications can cause decreased IQ scores in children whose mothers took them while pregnant.<sup>1</sup> Stronger warnings about use during pregnancy will be added to the drug labels, and valproate's pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug).

With regard to valproate use in pregnant women with epilepsy or bipolar disorder, valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder.

With regard to women of childbearing age who are not pregnant, valproate should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate products should use effective birth control.

Valproate products include: valproate sodium (Depacon), divalproex sodium (Depakote, Depakote CP, and Depakote ER), valproic acid (Depakene and Stavzor), and their generics.

This alert is based on the final results of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study showing that children exposed to valproate products while their mothers were pregnant had decreased IQs at age 6 compared to children exposed to other anti-epileptic drugs (see Data Summary).<sup>1</sup> The difference in average IQ between the children who had been exposed to valproate and the children who had been exposed to other antiepileptic drugs varied between 8 and 11 points depending on the drug to which valproate was compared.

FDA previously communicated initial findings about this risk in a [June 2011 Drug Safety Communication](#). At that time, FDA also worked with valproate manufacturers to revise the drug labels after interim results from the NEAD study showed lower cognitive test scores at age 3 in children exposed to valproate compared to children exposed to other antiepileptic drugs.<sup>2</sup>

Women who are pregnant and taking a valproate medication should not stop their medication but should talk to their health care professionals immediately. Stopping valproate treatment suddenly can cause serious and life-threatening medical problems to the woman or her baby.

It is not known whether there is a specific time period during pregnancy when valproate exposure can result in negative cognitive effects. Similarly, there is no known time during pregnancy in which exposure may be considered to have less risk for decreased IQ in children. Because the women in the NEAD study were exposed to antiepileptic drugs throughout pregnancy, whether the risk for decreased IQ was related to a particular time period during pregnancy could not be assessed.

FDA is working with manufacturers to change the drug labels for valproate products with this updated risk information. FDA continues to evaluate information about the potential risks of valproate use during pregnancy and will update the public as more information becomes available.

Pregnancy Category X means that studies in animals or humans have shown positive evidence of fetal risk, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefits. Category D means there is positive evidence of risk to a baby based on data from studies or other experience in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

### **Facts about Valproate**

- Valproate products are approved for the treatment of certain types of epilepsy, the treatment of manic episodes associated with bipolar disorder, and the prevention of migraine headaches. They are also used off-label (for uses not approved by FDA) for other conditions, particularly other psychiatric conditions.
- Valproate products include: valproate sodium (Depacon), divalproex sodium (Depakote, Depakote CP, and Depakote ER), valproic acid (Depakene and Stavzor), and their generics.
- In the outpatient retail setting in 2012, approximately 1.5 million patients received a dispensed prescription for valproic acid and derivative products, and approximately 22% (341,000 patients) of total patients were women of reproductive potential age (13-45 years).<sup>3</sup> According to office-based physician survey data for 2012, 57% of all drug use mentions for valproic acid and derivative products in women of reproductive potential age were associated with diagnoses of episodic mood disorders, 10% for the diagnoses of schizophrenic disorders, 9% for migraine, and 9% for epilepsy and recurrent seizures.<sup>4</sup>

### **Additional Information for Patients**

- Taking valproate during pregnancy can decrease your child's IQ. There is also a higher risk of birth defects if you take valproate during pregnancy.
- If you are a woman of childbearing age and are taking a valproate product, you should use effective birth control.

- If you are planning to become pregnant or if you are pregnant and taking a valproate product, you should talk to your health care professional right away.
- Do not stop taking valproate products without talking to your health care professional. Stopping such treatment suddenly can cause serious and life-threatening medical problems. For example, the sudden discontinuation of valproate in pregnant women with seizures can result in persistent seizures, which can cause harm, including death, to the mother and/or the unborn baby.
- Discuss any questions or concerns about valproate products with your health care professional.
- If you become pregnant while taking valproate, talk to your health care professional about registering with the North American Antiepileptic Drug Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy. You can enroll in this registry by calling 1-888-233-2334. Information on the registry can be found at <http://www.aedpregnancyregistry.org/>
- Taking folic acid supplements before getting pregnant and during early pregnancy has been shown to lower the chance of having a baby with a neural tube defect.
- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

#### **Additional Information for Health Care Professionals**

- Valproate products should not be used in pregnant women for prevention of migraine headaches.
- Valproate products should be used in pregnant women with epilepsy or bipolar disorder only if other treatments have failed to provide adequate symptom control or are otherwise unacceptable.
- Inform women of childbearing age of the increased risk for decreased IQ in children exposed to valproate products in utero.
- Valproate products should not be administered to a woman of childbearing age unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine).
- Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of valproate use during pregnancy, and alternative therapeutic options should be considered for these patients.

- It is not known whether the adverse effects on IQ are related to the timing or duration of exposure to valproate during pregnancy. Therefore, exposure to valproate at any time during pregnancy should be considered to have the potential to result in decreased IQ in children.
- Continue to counsel women of childbearing age taking valproate about the increased risk of other major structural and functional birth defects, particularly neural tube defects, when valproate is used during pregnancy.
- Dietary folic acid supplementation should be routinely recommended both prior to conception and during pregnancy for patients taking valproate because studies in the general population show that folic acid supplementation prior to conception and during early pregnancy reduces the risk of neural tube defects.
- To collect information on the effects of in utero exposure to valproate, physicians should encourage pregnant patients taking valproate products to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling toll free 1-888-233-2334, and must be done by the patients. Information on the registry can be found at <http://www.aedpregnancyregistry.org/>
- Report adverse events involving valproate products to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

### Data Summary

The NEAD study included mothers with epilepsy who were taking one of four different antiepileptic drugs as monotherapy: lamotrigine, carbamazepine, phenytoin, or valproate products<sup>1,2</sup> The study compared the results of IQ tests when children who had been exposed to antiepileptic drugs in utero were 6 years old. Interim cognitive assessments were also performed when the children were 3 years old and at other time points. The children exposed to valproate products during pregnancy had lower IQ scores at age 6 as shown in the table below, adapted from Meador et al., than children with prenatal exposure to the other antiepileptic drug monotherapy treatments. The differences between valproate and other monotherapy treatments are all statistically significant.

Drug	Valproate	Carbamazepine	Lamotrigine	Phenytoin
Number of children	62	94	100	55
Mean IQ (95% CI)	97 (94-101)	105 (102–108)	108 (105–110)	108 (104–112)

The mean IQs were higher in the overall group in children whose mothers reported periconceptional folate use. This finding should be interpreted with caution and regarded as preliminary because the

effect of periconceptional folate use was not a primary outcome of the study and information about its use and dose were collected retrospectively at the time of enrollment.

It is not known whether the timing of exposure during pregnancy affects the severity of cognitive effects in children. There is no known time during pregnancy in which exposure may be considered to have less risk for cognitive effects in children. The women in the NEAD study were exposed to antiepileptic drugs throughout their pregnancies.

The results of the NEAD study are consistent with those of other published epidemiological studies that have indicated that children exposed to valproate in utero have lower IQ scores than children exposed to either another antiepileptic drug in utero or to no antiepileptic drugs in utero.

Valproate products have long been known to increase the risk of serious birth defects, in particular, neural tube defects such as spina bifida. This risk is already described in detail in the drug labels for valproate products.

## **References**

1. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurology* 2013; 12 (3): 244-252.
2. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009; 360:1597-605.
3. IMS, Total Patient Tracker (TPT). July 2009 – June 2012. Extracted February 2013.
4. Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel. 2012. Extracted March 2013.