Drugs

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Information for Healthcare Professionals: Risk of Neural Tube Birth Defects following prenatal exposure to Valproate

For current information about Valproate products, please see
Valproate Information

[December 3, 2009]: The FDA is reminding health care professionals about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular malformations, in babies exposed to valproate sodiumand related products (valproic acid and divalproex sodium) during pregnancy. The FDA will be working with the manufacturers of these products to address labeling changes.

Healthcare practitioners should inform women of childbearing potential about these risks, and consider alternative therapies, especially if using valproate to treat migraines or other conditions not usually considered life-threatening.

Women of childbearing potential should only use valproate if it is essential to manage their medical condition. Those who are not actively planning a pregnancy should use effective contraception, as birth defect risks are particularly high during the first trimester, before many women know they are pregnant.

FDA has required a patient *Medication Guide* for each antiepileptic drug (AED), including valproate. The valproate *Medication Guide* will explain the benefits and risks of valproate and encourage patients to discuss options with their healthcare professional.

Valproate sodium is marketed as Depacon. Dilvalproex sodium is marketed as Depakote, Depakote CP, Depakote ER. Valproic acid is marketed as Depakene and as Stavzor.

Pregnant women using valproate or other AEDs should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (1-888-233-2334; www.aedpregnancyregistry.org).

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program using the information at the bottom of the page.

Background

FDA first approved Depakene (valproic acid) in 1978 for the treatment of epilepsy. More recently, FDA approved valproate for the treatment of bipolar disorder and migraine headaches. As valproate's indications for use expand, it is critical that all health care professionals caring for women of childbearing potential and taking valproate for any indication be informed that valproate causes an increased risk of major birth defects. Awareness of the therapeutic benefits and risks of valproate and alternative therapies, as well as the risks of untreated disease, is critical for informed prescribing and counseling of all women taking valproate.

Valproate and Birth Defect Risk

Valproate use during pregnancy increases the risk of major malformations, including neural tube defects. In the United States, about 1 in 1500 babies is born with a neural tube defect. The risk of neural tube defects is much higher in babies born to mothers treated with valproate during the first 12 weeks of pregnancy, with the risk increasing to 1 in 20 babies.

Data from the NAAED Pregnancy Registry show that the rate of major malformations in babies born to women with epilepsy taking valproate (monotherapy) is almost 4 times higher than the rate of major malformations in babies born to women with epilepsy taking a different antiepileptic drug. The NAAED Registry reported a major malformation rate of 10.7% (95% C.I. 6.3% – 16.9%) in the offspring of women exposed to an average of 1,000 mg/day of valproic acid monotherapy during pregnancy (dose range 500 – 2000 mg/day). The major malformation rate among the internal comparison group of 1,048 women with epilepsy who received any other antiepileptic drug monotherapy during pregnancy was 2.9% (95% CI 2.0% to 4.1%). Sixteen major

malformations occurred in the offspring of 149 women who used valproate during pregnancy, and these malformations included neural tube defects, craniofacial defects, cardiovascular malformations and malformations involving other body systems.

Folic Acid and Neural Tube Defects

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 ensure adequate folic acid intake, women of childbearing potential should use FDA approved folic acid prescription drugs and not rely on dietary intake or supplements alone.

Considerations for Health Care Professionals

- Valproate use during early pregnancy increases the risk of major malformations in the baby. The rates for neural tube defects in babies exposed to valproate during the first trimester are 30 to 80 times higher than the rate for neural tube defects in the general U.S. population. In pregnant women with epilepsy, valproate monotherapy is associated with a four-fold higher rate of major malformations than other antiepileptic drug monotherapies.
- Women of childbearing potential who are considering valproate therapy or who are taking valproate should be advised of both the risks of their medical condition and the medicines used to manage their condition.
- Healthcare professionals should counsel women of childbearing potential taking valproate about the increased risk of major malformations, including neural tube defects, when valproate is used during pregnancy.Healthcare practitioners should recommend use of effective contraception for women who are not planning a pregnancy and discuss the relative risk and benefits of appropriate alternative therapies.
- Untreated or inadequately treated epilepsy or bipolar disorder during pregnancy increases the risk of complications in both the pregnant mother and her developing baby.
- Healthcare professionals should inform patients that taking folic acid before and during the first trimester of pregnancy can decrease the risk for congenital neural tube defects.
- Available prenatal diagnostic testing to detect neural tube defects and other malformations should be offered to all women who become pregnant while taking valproate.
- Women who become pregnant while taking valproate or other antiepileptic drug (AEDs) are encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334. Information on the registry can also be found at the website www.aedpregnancyregistry.org. This registry gathers information about the effects of antiepileptic drugs during pregnancy.

Information for Patients:

- Using valproate during pregnancy increases the chance of having a baby with a birth defect. Neural tube defects, such as spina bifida, are the birth defects most often seen with valproate use in early pregnancy.These defects of the brain and spinal cord occur when the developing spinal canal does not close normally.
- For this reason, a woman of childbearing potential should generally not take valproate unless it is considered essential for her treatment. Women of childbearing potential are women who have passed puberty and have not passed through menopause and have not had their uterus or ovaries removed.
- Women of childbearing potential who do take valproate should use effective birth control (contraception) while taking valproate.
- Women who are planning a pregnancy or who become pregnant while taking valproate should contact their healthcare professionals immediately.They should talk to their healthcare professionals about the best way to treat their health conditions before and during pregnancy. Healthcare professionals may discuss other treatment options.
- Valproate should not be stopped without talking to a healthcare professional, even in pregnant women. Stopping valproate suddenly can cause serious problems. Not treating epilepsy or bipolar disorder can be harmful to women and their developing babies.
- Women who become pregnant while taking valproate or other antiepileptic drugs (AEDs) should consider enrolling in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Women can do this by calling the toll-free number 1-888-233-2334. This pregnancy registry gathers information about the safety of antiepileptic drugs during pregnancy.
- It is important to know that birth defects also occur in babies born to women who are not taking any medicines and who do not have other risk factors, but they occur less often (in about 3 out of every 100 babies).
- 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.
- Women should tell their healthcare professionals about all the medicines they take, including prescription and non-prescription medicines, vitamins, and herbal supplements, and should not start a new medicine without first talking with a healthcare professional.

Related Information

- **Valproate Information**

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax

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Regular Mail: Use postage-paid **FDA Form 3500**

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