HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

VALPROATE-CONTAINING MEDICINES: RECOMMENDATION TO FURTHER RESTRICT THE USE OF VALPROATE IN WOMEN AND GIRLS

A recent Europe-wide review of valproate-containing medicines* has recommended strengthening of restrictions for their use and further characterising the risk of birth defects and developmental disorders in the product information. It is now recommended that valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. There are already detailed warnings contained in product information for patients and prescribers on the potential for birth defects and developmental disorders in children born to women taking valproate during pregnancy, which will now be strengthened further.

Healthcare Professionals should be aware that:

- Children exposed *in utero* to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).
- Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Prescribers should carefully weigh the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.
- Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- All female patients should be informed of and understand:
  - the risks associated with valproate during pregnancy;
  - the need to use effective contraception;
  - the need for regular review of treatment;
  - the need to rapidly consult if a woman is planning a pregnancy or becomes pregnant.

The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed all the available data from pre-clinical studies, pharmacoepidemiological studies, published literature, and spontaneous reports and sought the views of Healthcare Professionals and patient experts on the awareness, understanding and communication of the risks associated with valproate *in-utero* exposure. These contributions fed directly into the review process.

Further details of the EU review are available from the HPRA website (www.hpra.ie).

Advice to Healthcare Professionals

Risk of abnormal pregnancy outcomes

- The risk of congenital malformations is approximately 10% while studies in preschool children exposed *in utero* to valproate show that up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems [1,2,3,4,5].
- Intelligence quotient (IQ) measured in a study of 6 year old children with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics [6].
- Available data show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population [7].
- Limited data suggests that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD) [8].
- Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of childbearing potential unless where other treatments are not tolerated or are ineffective.
- The balance of the benefits of treatment with valproate should be weighed against the risks when prescribing valproate-containing medicines for the first time, at routine reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.
- Women of child bearing potential who are treated with valproate must be advised to use effective contraception during treatment and should be fully informed of the potential risks for the unborn child if they become pregnant during treatment.

Treatment during pregnancy

- If a woman who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to switching to alternative treatments.

- If valproate treatment is continued during the pregnancy then the following advice should be followed:

  - Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder in female patients;

  - The lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day. Prolonged release formulations may be preferable to normal release formulations;

  - Specialised prenatal monitoring should be initiated in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformations;

  - Folate supplementation before the pregnancy may decrease the risk of neural tube defects however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure;

  - All female patients must be fully informed of the risks associated with valproate during pregnancy, the need to use effective contraception, the need for regular review of treatment and the need to urgently discuss with their doctor if she is planning a pregnancy or becomes pregnant.

The product information (Summary of Product Characteristics (SmPC) and package leaflet (PL)) for valproate containing products will be updated to include the revised restrictions for use, the strengthened warnings and the additional information on the risks related to exposure during pregnancy to better inform healthcare professionals and patients. Furthermore, educational materials (including materials particularly developed for patients) will be provided to all healthcare professionals in the EU and to women prescribed valproate to inform them of these risks.

Key messages

- Valproate should not be prescribed to female children, female adolescents, women of child bearing potential or pregnant women unless other treatments are ineffective or not tolerated.

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).

- Valproate treatment should only be commenced and supervised by a doctor experienced in managing epilepsy and bipolar disorder in female patients.

- Before initiating treatment, the balance of the benefits of treatment with valproate must be weighed against the risks. This should be considered at routine treatment reviews, when a female reaches puberty and when a woman plans a pregnancy or becomes pregnant.

- All female patients must be informed of and understand the risks associated with valproate during pregnancy and the steps to take if pregnancy occurs or is planned.

- The product information for valproate-containing medicines will be updated shortly and educational materials will be provided to all healthcare professionals and female patients in the EU.

*Further details on valproate-containing medicines are available at www.hpra.ie

References

1. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81(1):1-13.
2. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October;51(10):2058-65.
3. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96:643-647.
4. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009;360 (16): 1597- 1605.
5. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behavi(13):229-236.
6. Meador K et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 (NEAD study): a prospective observational study. Lancet Neurol. 2013 March;12(3): 244-252.
7. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013;309(16):1696-1703.
8. Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. Epilepsy Behav. 2011; 22(2):240-246.