



European Medicines Agency - Science, medicines, health

Valproate and related substances

CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls

Women to be better informed of risks of valproate use in pregnancy and need for contraception

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) a regulatory body representing EU Member States, has agreed to strengthen warnings on the use of valproate medicines in women and girls due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. The warnings aim to ensure that patients are aware of the risks and that they take valproate only when clearly necessary.

Doctors in the EU are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproate is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

Women and girls who have been prescribed valproate should not stop taking their medicines without consulting their doctor as doing so could result in harm to themselves or to an unborn child.

In countries where valproate medicines are also authorised for the prevention of migraine, valproate must not be used for this purpose in pregnant women, and doctors should exclude pregnancy before starting preventive treatment for migraine. Doctors must not prescribe valproate for migraine prevention for women who are not on effective contraception.

These recommendations follow a review of recent studies showing developmental problems in up to 30 to 40% of pre-school children exposed to valproate in the womb, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.^{1,2,3,4,5}

Previous data have shown that children exposed to valproate in the womb are also at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There are also limited data suggesting that children exposed to valproate in the womb may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).^{6,7,8}

In addition, children exposed to valproate in the womb are at an approximately 11% risk of malformations at birth (such as neural tube defects and cleft palate)⁹ compared with a 2 to 3% risk for children in the general population.

Doctors should ensure that their patients are adequately informed of the risks of taking valproate during pregnancy, and should regularly review the need for treatment in female patients who can have children. Doctors should also re-assess the balance of the benefits and

risks of valproate medicines for any female patient who becomes or plans to become pregnant and for girls reaching puberty.

The review of valproate was conducted by the EMA's Pharmacovigilance and Risks Assessment Committee (PRAC), following which the CMDh endorsed the PRAC's recommendations.

The recommendations on the use of valproate in women and girls will be implemented by EU Member States according to an agreed timetable.

¹Meador K, Reynolds MW, Crean S, *et al.* 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.

²Meador KJ, Penovich P, Baker GA, *et al.* Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009;15(3):339-43.

³Bromley RL, Mawer G, Clayton-Smith J, *et al.* Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 2008;71(23):1923-4.

⁴Cummings C, Stewart M, Stevenson M, *et al.* Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011 July;96(7):643-7.

⁵Thomas SV, Ajaykumar B, Sindhu K, *et al.* Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy Behav* 2008 Jul;13(1):229-36.

⁶Christensen J, Grønberg TK, Sørensen MJ, *et al.* Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013 Apr 24;309(16):1696-1703.

⁷Cohen MJ, Meador KJ, Browning N, *et al.* Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav* 2013;29(2):308-15.

⁸Cohen MJ, Meador KJ, Browning N, *et al.* Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. *Epilepsy Behav* 2011 Oct;22(2):240-6.

⁹Meador 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 Neurol* 2013;12(3):244-52.

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