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PRAC recommends strengthening the restrictions on the use of valproate in women and girls

Women to be better informed of the risks of valproate use during pregnancy

The EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) has recommended strengthening the restrictions on the use of valproate medicines due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Women for whom valproate is the only option after trying other treatments, should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

Women who have been prescribed valproate should not stop taking their medicine without first consulting their doctor.

In countries where valproate medicines are authorised for the prevention of migraine, women must not use valproate for preventing migraine when they are pregnant. Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.

The PRAC also recommended that doctors who prescribe valproate provide women with full information to ensure understanding of the risks and to support their decisions.

These recommendations follow a review of available data on the effects of valproate exposure during pregnancy. During the review the PRAC also consulted representatives of patients and families who have been affected as well as a group of experts and specialists. While valproate remains an option for patients where other treatments have failed or are not tolerated, the Committee concluded that women and healthcare professionals need to be better informed about the risks of valproate exposure in the womb and of the need for effective contraception.

Recent studies have shown a risk of developmental problems of up to 30 to 40% in 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.

In addition, data show that 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) compared to a 2 to 3% risk for children in the general population. Available data also show that children exposed to valproate in the womb are at increased risk of autistic spectrum disorder (around 3 times higher than in the general

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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).

The PRAC recommended that educational materials should be provided to all healthcare professionals in the EU and to women prescribed valproate to inform them of these risks. Doctors will be required to review the treatment of girls and women on a regular basis, including at puberty and when a woman plans to become pregnant. The PRAC emphasised that women should not stop taking valproate without first consulting their doctor.

The EU product information for healthcare professionals and patients is to be updated with the latest information and recommendations.

The recommendations of the PRAC will now be sent the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. In the meantime, women currently taking valproate who have any questions about their treatment should speak with their doctor.

More about the medicine

Valproate and related substances have been used in the EU since the 1960s to treat epilepsy and bipolar disorder. Some valproate medicines are also authorised in some EU Member States to prevent migraine headaches.

Valproate and related medicines have been authorised via national procedures in all EU Member States, and in Norway and Iceland, and are marketed under various name including Absenor, Convival Chrono, Convulex, Convulsofin Tabletten, Delepsine, Depakine, Deprakine, Diplexil, Dipromal, Epilim, Episenta, Epival, Ergenyl, Espa-Valept, Hexaquin, Leptilan, Micropakine L.P., Orfiril, Orlept, Petilin, Valberg, Valepil and Valhel.

More about the procedure

The review of valproate and related substances was initiated in October 2013 at the request of the UK under Article 31 of Directive 2001/83/EC following the publication of new data on the risks to children of valproate exposure in the womb.

The review was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As medicines containing valproate and related substances are all authorised nationally, the PRAC recommendation will be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

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