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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 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}

^{*} The Coordination Group for Mutual Recognition and Decentralised Procedures – Human



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 who reach 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.

Information to patients

- **Do not stop taking your valproate medicine without consulting your doctor as doing so could cause harm to you or an unborn child.**
- Valproate medicines can cause malformations and problems with early development of children if they are exposed to these medicines in the womb.
- If you can become pregnant, you should use an effective method of contraception. Speak to your doctor if you have any questions about which contraceptive method is appropriate for you.
- Tell your doctor at once if you become pregnant, think you might be pregnant or are planning to become pregnant. Your doctor will urgently review your treatment.
- If you have any questions about your treatment or contraception, speak to your doctor or pharmacist.

Information to healthcare professionals

Following an evaluation of the data on the risks of valproate use during pregnancy, the recommendations for the use of valproate in women and girls have been updated:

- For treatment of epilepsy and bipolar disorder in female patients who can have children
 - Only prescribe valproate medicines for epilepsy and bipolar disorder if other treatments are ineffective or not tolerated.
 - Advise patients taking valproate medicines about effective contraception during their treatment.
 - Ensure that the treatment of epilepsy or bipolar disorder is supervised by a doctor experienced in treating these conditions.
 - Consider alternative treatments if a female patient becomes or plans to become pregnant during valproate treatment. Regularly review the need for treatment and re-assess the balance of the benefits and risks for female patients taking valproate and for girls reaching puberty.
 - Inform patients of the risks of taking valproate during pregnancy.
- For migraine prevention (in countries where this use is authorised)

- Do not prescribe valproate for female patients who can have children if they are not using effective methods of contraception or if they are already pregnant – such use is now contraindicated.
- Exclude pregnancy before starting a female patient on preventive treatment for migraine.
- Stop valproate treatment in the event of pregnancy or if pregnancy is planned.
- Ensure that female patients who can become pregnant are aware that they must keep to their contraception throughout treatment.
- Inform patients of the risks of taking valproate during pregnancy.

Healthcare professionals in the EU will be sent a dear healthcare professional letter plus additional educational material concerning these recommendations.

References

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More about the medicine

Valproate medicines are used to treat epilepsy and bipolar disorder. In some EU Member States they are also authorised to prevent migraine headaches.

The active ingredients are listed on the packages as valproic acid, sodium valproate, valproate semisodium or valpromide.

Valproate medicines have been authorised via national procedures in all EU Member States and in Norway and Iceland. They are marketed under several brand names 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 medicines started in October 2013 at the request of the UK's Medicines and Healthcare products Regulatory Agency (MHRA) under Article 31 of Directive 2001/83/EC, following the publication of new data on the risks risk of malformations and developmental problems in babies exposed to valproate in the womb.

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

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

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