PRAC recommends strengthening the restrictions on the use of Valproate containing products in women and girls

15.10.2014 | Circular Number P24/2014

Information on Valproate®

- Valproate and related substances have been used in the EU since the 1960s to treat epilepsy, bipolar disorders and in some member states (not in Malta) to prevent migraine headaches.

- The exact way valproate works is not well understood, but it is thought to act by increasing the amount of a neurotransmitter (a substance that relays signals between nerve cells) called gamma-amino butyric acid (GABA), which may act as a mood stabiliser. Valproate may also work by preventing the passage of electrically charged sodium particles through tiny pores in the surface of cells, which has the effect of reducing excessive electrical activity in the brain.

- It has been known for some time that using anti-epileptic medicines in pregnant women increases the risk of birth defects in their children and that valproate medicines may be associated with a higher risk of certain birth defects than other anti-epileptic medicines. It has also been known that development may be delayed in children born to women who were treated with valproate medicines during pregnancy.

- The product information for valproate medicines in the EU contains information on their use and risks during pregnancy.

Information from the European Medicines Agency about the safety concern

The review of valproate medicines started a year ago in October 2013 and was triggered following the publication of new studies suggesting that in some children problems in development, including autism may be long-lasting. There was also a need to update the product information of these medicines to bring them in line with current evidence.

During the review the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) consulted representatives of patients and families who have been affected as well as a group of experts and specialists and concluded that while valproate remains an option for patients where other treatments have failed or are not tolerated, 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 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).

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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 of all valproate containing medicinal products is to be updated with the latest information and recommendations.

For more information on Valproate and the referral procedure please visit **www.ema.europa.eu**

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 Malta:

For doctors and patients

In line with the Pharmacovigilance Risk Assessment Committee's recommendation, 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. Healthcare professionals and patients can expect to receive educational materials on the use of valproate in women.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Valproate containing medicines. Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form or online at **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.

Prof. John J Borg PhD (Bristol)
Post-licensing Director

Healthcare professionals and patients are encouraged to regularly check the Medicine Authority website for product safety updates as these are issued on an ongoing basis.

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