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Questions and answers on the review of medicines containing valproate for use in bipolar disorder

The European Medicines Agency has completed a review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of valproate in this condition outweigh their risks, and that all marketing authorisations for medicines containing valproate throughout Europe should be amended to include the treatment of manic episodes in bipolar disorders when lithium is contraindicated or not tolerated.

The review was carried out under an 'Article 31' referral¹.

What is valproate?

Valproate is a salt (sodium or semisodium) of valproic acid, an anti-epileptic medicine which can also be used in patients with bipolar disorder. This is a mental illness causing alternating periods of high mood (mania) and depression. The exact way valproic acid works is not fully understood, but it is known to increase the activity of the neurotransmitter gamma-amino butyric acid (GABA), by increasing the amount of GABA available in the gaps between nerve cells. Neurotransmitters are chemicals that allow nerve cells to communicate with each other. An increase in GABA in the brain is linked to mood stabilisation, and this helps to control the manic episodes (extremely high mood) associated with bipolar disorder.

Medicines containing valproate have been available since the mid-1960s. They are marketed in all European Union (EU) Member States under various trade names including Depakine/Deprakine, Depakote and Epilim, and as generic medicines.

Why was the use of valproate in bipolar disorder reviewed?

On 15 April 2008, the company that markets Valproat Ratiopharm Chrono, a generic medicine containing valproate used as anti-epileptic, applied to the German medicines regulatory agency to extend its use to include the 'acute treatment of manic episode and prevention of recurrence in patients with bipolar disorder'. This extension was in line with the reference medicine on which the

¹ Article 31 of Directive 2001/83/EC as amended, referral under Community interest.

generic medicine is based. However, on 9 March 2009, the Dutch medicines regulatory agency raised an objection to this change². The concern was that the data presented to support this use were too limited.

On 16 April 2009, the Dutch agency also raised general concerns on the effectiveness and safety of valproic acid and valproate in this indication, noting that there were differences among Member States in the marketing authorisations for this indication. Therefore, it asked the CHMP to carry out a full assessment of the benefit-risk balance of valproic acid and valproate in the treatment and prevention of manic episodes in bipolar disorder and to issue an opinion on whether the marketing authorisations for products containing valproate should be changed across the EU.

Which data has the CHMP reviewed?

The Committee reviewed the information supplied by the companies that make valproate-containing medicines to support the use of valproate-containing medicine in bipolar disorders. This included published articles reporting the results of 16 clinical studies of valproate in acute mania (either on its own or in combination) and in the prevention of recurrence of mood episodes in bipolar disorder.

What are the conclusions of the CHMP?

The CHMP noted that 25 Member States had authorised the indication in the EU. The studies presented by the companies show some evidence that valproate is effective in the acute treatment of manic episode, as seen in placebo controlled studies of three-week duration. The evidence for the use of valproate in maintenance treatment for the prevention of acute mania episode is more limited, as there is not comparison with placebo. Overall, the data are not sufficient to support the use of valproate as a first-line treatment. The CHMP recommended the use of valproate for the treatment of manic episode in bipolar disorder in patients who cannot take lithium (another medicine used in bipolar disorders).

Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of valproate-containing medicines in the management of manic episodes in bipolar disorder when lithium is contraindicated or not tolerated continue to outweigh its risks, and therefore recommended that all marketing authorisations for these medicines be varied either to include or to amend the indication. The Committee also concluded that the indication for the prevention of recurrence of mood episodes was not justified by the submitted data.

However, continuation of treatment after the manic episode can be considered in patients who have responded well to valproate.

This change also applies to generic medicines, including Valproat Ratiopharm Chrono.

Because bipolar disorder occurs mainly in adult patients, the change is not applicable to liquid formulations of valproate for use in children.

The European Commission issued a decision on 26 August 2010.

² This objection was raised as a referral under Article 6(12) of Regulation (EC) 1084/2003 as amended, referral on a variation to a marketing authorisation.

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