

Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations subject to conditions and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Scientific conclusions and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CMDh considered the below PRAC recommendation with regard to valproate and related substances-containing medicinal products:

1 - PRAC recommendation

Overall summary of the scientific evaluation by PRAC

The PRAC reviewed all available data from pre-clinical studies, pharmacoepidemiological studies, published literature, spontaneous reports as well as the views of the relevant experts (i.e. in neurology, psychiatry, child neuropsychiatry, obstetrics etc.) on the safety and efficacy of valproate and related substances in female children, women of childbearing potential and pregnant women. In addition, the views of patients, families and carers, and the view of healthcare professionals regarding the implications, the understanding and awareness of the risks associated with valproate in utero exposure were taken into account in the recommendation.

The review confirms the already known teratogenic risks associated with the use of valproate in pregnant women. Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29)¹. This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. The incidence of risk appears to be higher with valproate than with other antiepileptics.

Available data show an increased incidence of minor and major malformations in children born to mothers treated with valproate and related substances during pregnancy. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems^{2,3,4,5}.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.

¹ Meador K, 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.

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

³ Bromley RL et al.; Liverpool and Manchester Neurodevelopment Group. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology.* 2008; 71(23):1923-4.

⁴ Thomas SV et al. Intellectual and language functions in children of mothers with epilepsy. *Epilepsia.* 2007 Dec; 48(12): 2234-40.

⁵ Cummings C et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child.* 2011; 96(7): 643-7.

Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ⁶.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)^{7,8,9}.

The PRAC noted that valproate is considered to be an effective drug in the treatment of epilepsy and of manic episode in bipolar disorder, serious conditions that might be life threatening if not adequately controlled. Based on clinical data and also the views of the relevant experts it was concluded valproate should remain an option for female patients, but should be reserved for situations when other treatment alternatives have been tried and failed. Therefore, the PRAC concluded that valproate and related substances should not be used in female children, women of childbearing potential and pregnant women for the treatment of epilepsy and manic episode in bipolar disorder unless alternative treatments are ineffective or not tolerated.

The PRAC noted that in some Member States valproate is authorised for the prevention of migraine attacks. In view of the risks of valproate use during pregnancy and the available therapeutic alternatives for the treatment of acute migraine attacks, the PRAC concluded that in prophylaxis of migraine attacks valproate should be contraindicated in pregnancy or in women of childbearing potential who are not using effective methods of contraception.

The PRAC noted the concerns raised from patients about a lack of awareness on the risks associated with valproate in utero exposure. The PRAC agreed that targeted and appropriate information to healthcare professionals and patients were key to ensure a full understanding of the risks and that appropriate materials should be put in place.

In this respect, the PRAC recommended amendments to the product information, including strengthening of the wording to reflect the current knowledge of risks of developmental disorders and congenital anomalies and communication to healthcare professionals through a direct healthcare professional communication. In addition, the PRAC recommended education materials to be put in place in order to ensure that healthcare professionals and patients are informed about the risks associated with valproate in pregnant women and women of childbearing potential and on the measures necessary to minimise the risk. These include a prescriber guide, patient booklet and information ensuring the understanding and the awareness of prescribers and patients on the risks.

The PRAC also imposed a drug utilisation study to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate.

⁶ Meador KJ et al; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013; 12(3): 244-52.

⁷ Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA.* 2013; 309(16): 1696-703.

⁸ Cohen MJ et al; NEAD study group. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav.* 2013; 29(2): 308-15.

⁹ Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. *Epilepsy Behav.* 2011; 22(2): 240-246

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for valproate and related substances-containing medicinal products.
- The PRAC considered the totality of the data submitted with regard to safety and efficacy in female children, women of childbearing potential and pregnant women treated with valproate and related substances. This included the responses submitted by the marketing authorisation holders in writing and at oral explanation, as well as the outcome of the scientific advisory group in neurology. In addition, the PRAC considered the views of patients, families and carers, and the views of healthcare professionals for the understanding and the awareness of the risks associated with valproate in utero exposure.
- The PRAC considered that intra-uterine exposure to valproate and related substances is associated with an increased risk of developmental disorders in the offspring. The PRAC also confirmed the known risk of congenital anomalies.
- The PRAC concluded that valproate and related substances should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated in the following indications:
 - Treatment of primary generalised epileptic seizures, secondary generalised epileptic seizures and partial epileptic seizures;
 - Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania.
- The PRAC concluded that valproate and related substances should be contraindicated in prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception during treatment with valproate.
- The PRAC recommended further changes to the product information such as warnings and precautions and updated information on the risks related to exposure during pregnancy to better inform the healthcare professionals and women.
- The PRAC also concluded that there was a need for further risk minimisation measures such as educational materials aimed to better inform patients and healthcare professionals on the risks and a drug utilisation study to assess the effectiveness of the proposed risk minimisation measures. Core elements of a direct healthcare professional communication (DHPC) were agreed, together with the timelines for its distribution.

Therefore, the PRAC recommends the variation to the terms of the marketing authorisation for the valproate and related substances containing medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation.

The Committee, as a consequence, concluded that the benefit-risk balance of valproate and related substances-containing medicinal products, remains favourable subject to the conditions to the marketing authorisations, and taking into account the amendments to the product information, where applicable, and other risk minimisation measures recommended.

2 – Detailed explanation of the scientific grounds for differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, the CMDh emphasised that the referral procedure focussed on the risks associated with valproate and related substances in pregnant women and women of childbearing potential; the benefit-risk balance of valproate and related substances was assessed only in this subpopulation, and not in the general patient population for all indications.

The CMDh considered that the timeline for the submission of the drug utilisation study protocol should be extended in order to allow MAHs to perform a joint post-authorisation study (see Annex IV). In addition, the CMDh clarified that the study should be conducted in more than one Member State.

The CMDh also proposed a new timeline for the circulation of the DHPC in order to have it available to relevant recipients as soon as possible.

The CMDh included a clarification about the population affected by the recommendations as these are also applicable to female adolescents (aged between 12 to 16-18 years) according to the ICH E11 age classification of the paediatric population¹⁰.

The CMDh included a clarification on the use of prolonged release formulation to avoid high peak plasma concentrations in the summary of product characteristics.

The CMDh also considered the need to review the first part of the package leaflet for clarity reasons. The previous statements warning against the risks associated with valproate during pregnancy were summarised and included in rectangle frame. This follows the format used in the summary of product characteristics.

Minor editorial amendments were also introduced in the rest of the product information for clarity.

CMDh agreement

The CMDh, having considered the PRAC recommendation dated 9 October 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, agreed on the variation to the terms of the marketing authorisations of valproate and related substances containing medicinal products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.

The timetable for the implementation of the agreement is set out in Annex V.

¹⁰ ICH. Clinical Investigation of Medicinal Products in the Pediatric Population E11. Current Step 4 version dated July 2000.