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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 31 of Directive 2001/83/EC resulting from
pharmacovigilance data

Substances related to valproate

International non-proprietary name(s): sodium valproate, valproic acid,
valproate semisodium, valpromide

Procedure number: EMEA/H/A-31/1387

Note

Assessment report as adopted by the PRAC and considered by the CMDh with
all information of a commercially confidential nature deleted.



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1. Background information on the procedure

On 7 October 2013, further to the emergence of new evidence from the scientific literature on risks of developmental disorders in children exposed in-utero to valproate and related substances, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) triggered a referral under Article 31 of Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on whether the balance of benefits and risks for these products is still positive in the approved indications, in female children, women of child bearing potential and pregnant women and whether the marketing authorisation for valproate and related substances should be maintained, varied, suspended or revoked. As the request resulted from the evaluation of data resulting from pharmacovigilance activities, the PRAC issued a recommendation to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

After reviewing all the available data to address the concerns discussed, the PRAC adopted its recommendation on 9 October 2014.

2. Scientific discussion

Valproate and related substances (valproic acid, sodium valproate, valproate semisodium, and valpromide) are indicated since 1967 to treat epilepsy and since 1995 to treat bipolar disorders in Europe. In 2009, the bipolar disorders indication was restricted to the treatment of manic episode when lithium is contraindicated or not tolerated. For some patients with serious conditions, valproate is the only treatment option in these indications. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

Valproate and related substances have been authorised via national procedures in all EU Member States, and in Norway and Iceland.

The exact way valproate works is not fully understood, but it is thought to act by increasing the level of the neurotransmitter gamma-aminobutyric acid (GABA), which may act as a mood stabiliser. Valproate may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels, which has the effect of reducing excessive electrical activity in the brain.

It is known that using anti-epileptic medicines in pregnant women increases the risk of birth defects in their children and that valproate containing medicines are associated with a higher risk of certain birth defects than other anti-epileptic medicines¹. Data have also suggested an association between in-utero exposure to valproate and the risk of developmental disorders (frequently associated with craniofacial abnormalities), particularly of verbal intelligence quotient (IQ).

Following the European review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorders in 2009, the product information of valproate was updated to reflect the risks relating to the use during pregnancy, including the risk of birth defects and also the risk of developmental delay. The product information also states that valproate should not be used to treat epilepsy or bipolar disorders during pregnancy and in women of childbearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated).

It is only in recent years that new studies have become available that allow for robust evaluation of any possible risk of longer term developmental effects in children born to women treated with

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.

valproate^{2,3,4,5}. Although the product information for valproate medicines in the EU contains information on their use during pregnancy, the information regarding the association between valproate exposure and long term developmental disorders does not fully reflect the findings of these recent studies.

In light of the above, the MHRA decided to initiate a procedure under Article 31 of Directive 2001/83/EC on 7 October 2013, referring the matter to the PRAC and requesting the Committee to issue a recommendation on the benefit-risk of valproate and related substances in female children, women of childbearing potential and pregnant women and whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure.

The present review focus on the risks associated with valproate and related substances in pregnant women and women of childbearing potential.

2.1. Non-clinical aspects

2.1.1. Biological mechanisms

The specific mechanism through which valproate causes teratogenic effects, ranging from neural tube defects and other congenital malformations, and cognitive impairment, autism and autism spectrum disorder (ASD) has not been clearly defined. However, there is evidence from data generated in animal models and in vitro studies demonstrating the ability of valproate to interfere with a number of key embryonic developmental programmes whose impairment may explain the major structural defects and cognitive impairment characteristic of valproate teratogenicity (e.g. histone deacetylase (HDAC) inhibition, oxidative stress induction and disruption of folate metabolism) (Wilffert, 2011⁶; Kishi, 1997⁷).

The mechanism by which valproate exposure preferentially affects verbal skills is also not known at this point in time. Possible explanations include a general effect of altered gene expression during neurogenesis on more complex cognitive functions such as language by subtle defects in neuronal networks (Gervain, 2013⁸), or a differential effect of HDAC inhibition on the expression of exceptionally long genes, which are enriched in ASD-associated genes (King, 2013⁹).

The characteristic features of the cognitive impairment and structural malformations of valproate exposed offspring are also likely to be due to the complexity of the developmental process involved and its sensitivity to perturbations. Researchers have also shown that valproate is capable of causing altered neuronal morphology via myo-inositol depletion (Shaltiel, 2007¹⁰).

² Meador KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013; 12(3):244-52.

³ Bromley RL et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry.* 2013; 84(6):637-43.

⁴ Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA.* 2013; 309(16):1696-703.

⁵ Veiby G et al. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia.* 2013; 54(8):1462-72.

⁶ Wilffert B et al. Pharmacogenetics of drug-induced birth defects: what is known so far? *Pharmacogenomics.* 2011; 12:547-58.

⁷ Kishi T et al. Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy, *Journal of the Neurological Sciences.* 1997; 145: 109-12.

⁸ Gervain J et al. Valproate reopens critical-period learning of absolute pitch. *Frontiers in Systems Neuroscience.* 2013; 7: 1-11.

⁹ King IF et al. Topoisomerases facilitate transcription of long genes linked to autism. *Nature.* 2013 Sep 5; 501(7465):58-62.

¹⁰ Shaltiel G et al. Specificity of mood stabilizer action on neuronal growth cones. *Bipolar Disord.* 2007 May; 9(3):281-9.

The biological basis for the susceptibility of valproate teratogenesis would appear to be multifactorial where extrinsic factors (e.g. dose-response/plasma concentrations, length and timing of gestational exposure (stage of embryogenesis)) and intrinsic factors (e.g. effect on key developmental programmes, folate antagonism, presence of polymorphisms), are likely to define the outcome of exposures on an inter-individual basis.

A review on the relation between valproate use and autism spectrum disorders provides some insights into the biological mechanisms behind the association that are summarised in the following figure 1 (adapted from Chomiak, 2013¹¹).

Figure 1: Key molecular and cellular changes associated with valproate (adapted from Chomiak et al, 2013)

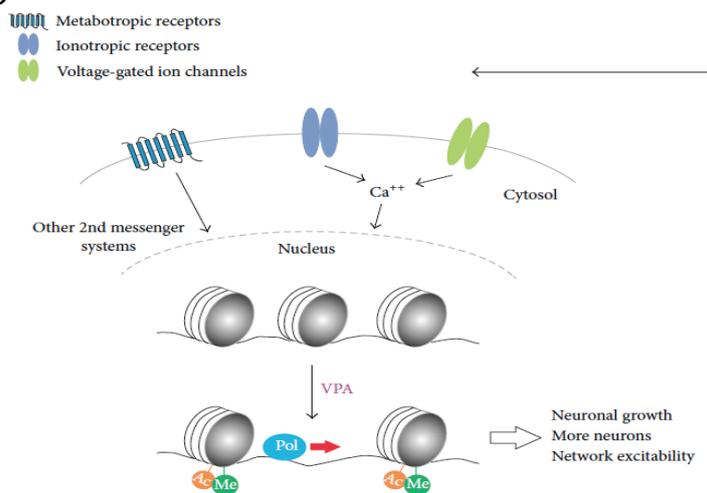


FIGURE 1: A schematic of some key molecular and cellular changes associated with VPA related to ASD neuropathology. Common clinicopathology associated with ASD is accelerated or early brain overgrowth and increased network excitability. Early or accelerated overgrowth may result from more synapses, increased dendritic growth, and/or increased number of cells, while increased network excitability may result from hyperconnectivity and/or hyperplasticity of microcircuits, presumably driven by synaptic mechanisms (i.e., enhanced paired-pulse facilitation and long-term potentiation) that have been shown in rat brain both *in vitro* and *in vivo* following prenatal VPA exposure [56, 57]. All of these aspects are also likely regulated by histone acetylation (orange circles "Ac") and/or histone methylation (green circles "Me") and possibly DNA methylation (DNA methylation not shown). VPA has been shown to increase histone acetylation and histone methylation that can promote gene activation (symbolized by blue circle "Pol"; RNA polymerase). While VPA may disrupt the balance between excitatory and inhibitory neuronal activities through histone acetylation modulation [58], the role of histone methylation on VPA-related ASD neuropathology is much less clear. Increased connectivity and network excitability may further influence this process by activating metabotropic, ionotropic, and voltage-gated ion channels and subsequent intracellular signaling cascades.

2.1.2. Pre-clinical studies

Information on incidence of congenital malformations related to plasma peak was published in the literature (Nau, 1981¹²; Nau, 1985¹³). The most prominent malformations lesions observed in mice were *spina bifida* and exencephaly. By comparing different administration regimen (once daily, multiple injections per day and infusion), Nau et al. (1981, 1985) also showed that the total plasma concentration was the crucial determinant for the teratogenicity of valproate in mice. However, it is noted that the major differences between the pharmacokinetics of valproate in animals (mice) and humans should be taken into account in any extrapolation of the data.

¹¹ Chomiak T et al. What We Have Learned about Autism Spectrum Disorder from Valproic Acid? Pathology Res. Intl. 2013; 1-8.

¹² Nau H et al. A new model for embryotoxicity testing. Teratogenicity and pharmacokinetics of valproic acid following constant rate administration in the mouse using human therapeutic drug and metabolites concentrations. Life Science 1981; 29: 2803-14.

¹³ Nau H. Teratogenic valproic acid concentrations: infusion by implanted minipumps vs conventional injection regimen in the mouse. Toxicology and Applied Pharmacology. 1985; 80: 243- 50.

Dencker et al. (1990)¹⁴ also found that high peak plasma concentration (C_{max}) for valproate correlates with the incidence of neural tube defects in mice. This may be explained by saturation of plasma protein binding sites, increased amount of unbound drug available for placental diffusion and accumulation of drug in embryonic neuroepithelium.

Several authors published that, in mice, when high teratogenic dosages were divided into several portions (thus lower peak concentrations), the teratogenic effect was reduced (Davis, 1994¹⁵; Nau, 1981; Nau, 1985). Embryofetotoxicity characterised as increased resorptions (embryonic loss) and reduced fetal growth were associated with chronic exposures at lower doses (AUC).

The relevance of these findings to humans is unclear particularly as the differences in the sensitivity of humans to valproate induced major congenital malformations compared to mice is unknown and the pharmacokinetics of valproate in mice is significantly different to that of humans.

Several rodent studies have shown that prenatal valproate exposure can lead to behavioural abnormalities that seem similar to those observed in autistic patients; including decreased social interaction and sensitivity to pain, increased sensitivity to non-painful stimuli, repetitive/stereotypic-like activity, increased anxiety, abnormally high and longer lasting fear memories, and changes in pup ultrasonic vocalisations.

A specific dose threshold for increased incidence of autism-like behaviours has not been clearly identified (Roullet, 2013¹⁶).

2.2. Clinical aspects

2.2.1. Patient exposure

The number of treatment-years by country and indication in female patients aged 15-49 years from 2010 to 2012 was calculated by using Intercontinental Marketing Services (IMS) data. The number of exposed patients has not been estimated, as the mean duration of treatment was not available.

For five EU Member States during last trimester of 2010 through 2012 between 14.7% and 26.6% of the prescriptions concerned female patients between 15-49 years of age.

In four of these European Member States, valproate and valpromide (pro-drug of valproate) were mainly prescribed for epilepsy, with rates varying between 41.9% to 71.1% in female patients aged between 15-49 years. In one Member State, however, the rate for epilepsy was 3.9% with the highest prescription rate recorded in bipolar disorders (63.1% in female patients aged 15-49 years from 2010 to 2012).

2.2.2. Safety

In its assessment, the PRAC considered all the data submitted in relation to the safety of valproate in female children, women of childbearing potential and pregnant women to the Committee from different sources. A summary of the most relevant data is included below.

¹⁴ Dencker L et al. Marked accumulation of valproic acid in embryonic neuroepithelium of the mouse during early organogenesis. *Teratology* 1990; 41: 699-706.

¹⁵ Davis R et al, Valproic acid A Reappraisal of its Pharmacological Properties and Clinical Efficacy in Epilepsy. *Drugs*. 1994; 47(2): 332-72.

¹⁶ Roullet FI et al. In utero exposure to valproic acid and autism—a current review of clinical and animal studies. *Neurotoxicol Teratol*. 2013; 36: 47-56.

2.2.2.1. Pharmacoepidemiological studies/ registries

Congenital malformation - Meador et al. 2008

Data from the meta-analysis by Meador et al. (2008) quantifies the incidence of congenital malformations associated with in utero antiepileptic drug exposure. This meta-analysis of 59 pregnancy registries and cohort studies involved over 65,000 pregnancies in women with epilepsy and over 1.8 million pregnancies in healthy women. The authors estimated the incidence rates associated with exposure to different antiepileptic drugs regimens, as monotherapy and polytherapy (i.e. combining two or more antiepileptic drugs).

The results are presented in the Table 1.

The total number of polytherapies combining three antiepileptic drugs including valproate, is very limited and the observed incidence rate of 25.00 (5.97-44.3) should be interpreted with caution.

Table 1: Incidence of congenital malformations by antiepileptic drugs exposure

Treatment regimen	Malformations t (n)	% [95%CI]
Women without epilepsy	9 (108,084)	3.27 [1.37, 5.17]
Monotherapy		
Carbamazepine	24 (4,411)	4.62 [3.48, 5.76]
Lamotrigine	5 (1,337)	2.91 [2.00, 3.82]
Phenobarbital	14 (945)	4.91 [3.22, 6.59]
Phenytoin	16 (1,198)	7.36 [3.60, 11.11]
Valproate	19 (2,097)	10.73 [8.16, 13.29]
Polytherapy-2 drugs		
Carbamazepine + 1 other	25 (942)	7.10 [3.71, 10.49]
Lamotrigine + 1 other	5 (599)	5.59 [1.11, 10.08]
Phenobarbital + 1 other	19 (603)	9.19 [5.88, 12.50]
Phenytoin + 1 other	18 (720)	11.47 [6.65, 16.30]
Valproate + 1 other	14 (694)	9.79 [7.57, 12.02]
Polytherapy-3 drugs or more		
Carbamazepine + 2 or more others	4 (70)	8.57 [1.99, 15.16]
Lamotrigine + 2 or more others	-	-
Phenobarbital + 2 or more others	6 (221)	14.57 [8.81, 20.33]
Phenytoin + 2 or more others	9 (276)	14.27 [8.95, 19.60]
Valproate + 2 or more others	2 (20)	25.00 [5.97, 44.03]

t = number of treatment arms reporting characteristic. *n* = number of patients reporting characteristic. CI = 95% confidence interval, %=n/N.

The findings of this study are reflected in the current valproate product information with specific reference to the 10.73% risk associated with valproate. This meta-analysis provides robust evidence

on the incidence of malformations. The incidence associated with valproate monotherapy is clearly significantly higher than for carbamazepine, lamotrigine, and phenobarbital.

Several studies^{17,18,19,20,21,22,23,24} suggested that the teratogenic risk of valproate increases with increasing dose.

Impaired cognitive development

Several observational prospective and retrospective studies investigating impaired cognitive development with use of valproate in pregnancy were reviewed^{25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48}.

¹⁷ Bromfield EB et al. Valproate teratogenicity and epilepsy syndrome. *Epilepsia*. 2008;49(12):2122-4.

¹⁸ Lindhout D et al. Spectrum of neural-tube defects in 34 infants prenatally exposed to antiepileptic drugs. *Neurology*. 1992;42(Suppl. 5):111-8.

¹⁹ Omtzigt JG et al. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology*. 1992 Apr;42(4 Suppl 5):119-25

²⁰ Diav-Citrin O et al. Pregnancy outcome after in utero exposure to valproate : evidence of dose relationship in teratogenic effect. *CNS Drugs* 2008; 22(4): 325-34.

²¹ Tomson T et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011;10(7):609-17.

²² Kaneko S et al. Congenital malformations due to antiepileptic drugs. *Epilepsy Res*. 1999;33(2-3):145-58.

²³ Mawer G et al. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. *Seizure* 2002; 11(8): 512-8.

²⁴ Vajda FJ et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol*. 2006 Jun;13(6):645-54.

²⁵ Meador KJ et al; For the NEAD Study Group. Effects of fetal antiepileptic drug exposure: Outcomes at age 4.5 years. *Neurology*. 2012 Apr 17;78(16):1207-14.

²⁶ Meador KJ et al; NEAD Study Group. Antiepileptic drug use in women of childbearing age. *Epilepsy Behav*. 2009;15(3):339-43

²⁷ 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.

²⁸ Cohen MJ et al; NEAD study group. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. *Epilepsy Behav*. 2013;29(2):308-15.

²⁹ Bromley RL et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010;51(10):2058-65.

³⁰ 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.

³¹ Bromley RL et al; Liverpool and Manchester Neurodevelopment Group. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry*. 2013 Jun;84(6):637-43.

³² Shallcross R et al. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 2011 January 25;76(4):383-9.

³³ Shallcross R et al The cognitive and language abilities of children exposed in utero to levetiracetam and sodium valproate: 3–4 years of age. *Epilepsia* 2011 52 SUPPL. 6 (30) (abstract presented at 29th International Epilepsy Congress, Rome, 28 August–1 September 2011)

³⁴ Cummings C et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011 July;96(7):643-7.

³⁵ Thomas SV et al. Intellectual and language functions in children of mothers with epilepsy. *Epilepsia*. 2007 Dec;48(12):2234-40.

³⁶ Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy Behav*. 2008 Jul;13(1):229-36.

³⁷ Nadebaum C et al. The Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. *J Int Neuropsychol Soc* 2011 January;17(1):133-42.

³⁸ Nadebaum C et al. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology*. 2011 Feb 22;76(8):719-26.

³⁹ Gaily E et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology*. 2004 Jan 13;62(1):28-32.

⁴⁰ Eriksson K et al. Children exposed to valproate in utero-population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res*. 2005 Jul;65(3):189-200.

⁴¹ Titze K et al. Prenatal and family risks of children born to mothers with epilepsy: effects on cognitive development. *Dev Med Child Neurol*. 2008 Feb;50(2):117-22.

⁴² Veiby G et al. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia*. 2013 Aug;54(8):1462-72.

⁴³ Veiby G et al. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol*. 2013 Nov 1;70(11):1367-74.

⁴⁴ Vinten J et al; Liverpool and Manchester Neurodevelopment Study Group. Neuropsychological effects of exposure to anticonvulsant medication in utero. *Neurology*. 2005 Mar 22;64(6):949-54.

⁴⁵ Adab N et al. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2001 January;70 (1): 15-21.

Studies in children of mothers with epilepsy demonstrated that exposure to valproate during pregnancy was associated with impaired cognitive development in infants, reduced intellectual functioning and autism spectrum disorders. These studies also confirmed the high correlation between maternal IQ and education and child IQ or cognitive outcome (Meador, 2011). It is noted that these studies have their inherent strengths and limitations.

The magnitude of risk of cognitive impairment and autism spectrum disorders varies across studies. Studies in preschool children exposed in utero to valproate show that up to 30-40% have delays in their early development such as talking, and/or walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems^{26, 30, 34, 36}. There are limited data on the long term outcomes.

The results of the two main studies (Meador, 2013; Christensen, 2013) are presented below.

- Meador et al. 2013 (Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study)

The NEAD Study was a pivotal prospective observational, assessor-masked, multicentre study, which enrolled pregnant women with epilepsy on antiepileptic drug monotherapy (carbamazepine, lamotrigine, phenytoin, or valproate) between October, 1999, and February, 2004, at 25 epilepsy centres in the UK and the USA. Planned analyses were conducted using Bayley Scales of Infant Development (BSID at age 2) and Differential Ability Scale (IQ at ages 3 and 4.5).

The primary analysis of the study by Meador et al. (2013), included 305 mothers and 311 children (6 twin pairs). 224 children completed 6 years of follow-up. The findings at age 6 years were in line with the findings at younger ages. Therefore, only the results at age 6 are presented below (Meador, 2013).

Results

Follow-up at age 6 showed that the IQ of children born to women with epilepsy on antiepileptic drug monotherapy was lower after exposure to valproate (mean 97, 95% CI 94-101) than to carbamazepine (105, 102-108; $p=0.0015$), lamotrigine (108, 105-110; $p=0.0003$), or phenytoin (108, 104-112; $p=0.0006$). Age-6 IQ correlated with IQs at younger ages (2, 3, and 4.5 years), and IQ improved with age for infants exposed to any antiepileptic drug.

Higher doses of valproate were associated with lower IQs at age 6 than lower doses (Doses above median dose (1000mg/day) - Mean IQ: 94, 95% CI: 90-99 vs. Doses below median dose - Mean IQ: 104, 95% CI: 99-109, $p\text{-value}=0.0065$).

Children exposed to valproate did poorly on measures of verbal and memory abilities compared to those exposed to the other antiepileptic drugs and on non-verbal and executive functions compared to lamotrigine (but not carbamazepine or phenytoin).

High doses (doses above median dose (1000mg/day) of valproate were negatively associated with IQ ($r=-0.56$, $p=0.0001$), verbal ability ($r=-0.40$, $p=0.0045$), non-verbal ability ($r=-0.42$, $p=0.0028$), memory ($r=-0.30$, $p=0.0434$), and executive function ($r=-0.42$, $p=0.0004$), but other antiepileptic drugs were not correlated at any dose.

The conclusion of the authors (Meador, 2013) is that fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains at 6 years of age albeit in

⁴⁶ Adab N et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2004 Nov; 75(11): 1575-83.

⁴⁷ Dean JC et al. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet*. 2002 Apr; 39(4): 251-9.

⁴⁸ Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA*. 2013 Apr 24; 309(16): 1696-703.

relatively small numbers of children. The authors postulate that reduced right handedness and verbal (vs. non-verbal) abilities might be attributable to changes in cerebral lateralisation induced by exposure to antiepileptic drugs.

Cohen et al.⁴⁹ reported on adaptive and behavioural function in children from the NEAD study at 3 years of follow-up. The authors concluded that on the basis of parent ratings of attention span and hyperactivity, children of mothers who took valproate during pregnancy are at a significantly greater risk for a future diagnosis of attention deficit hyperactivity disorder (ADHD) (23.3% of children at 3 years of age exposed in utero to valproate were at risk for ADHD).

Follow-up at age 6 was in line with previous findings (Cohen, 2013). Based upon Behaviour Assessment System for Children (BASC) by parent and teacher ratings of attention span and hyperactivity, children of mothers who took valproate during pregnancy were at a significantly greater risk for a diagnosis of ADHD (21.4% of children at 6 years of age exposed in utero to valproate were at risk of ADHD).

Both percentages were significantly greater than the national Center for Disease Control and Prevention estimate (7% - 9% in children aged between 5 and 17 years) for children in the general population⁵⁰.

The PRAC considered that the NEAD study provides robust data to show that the 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. Although the role of confounding factors cannot be excluded, there is evidence that the risk of intellectual impairment may be independent from maternal IQ in children exposed to valproate.

- Christensen et al. 2013

The Christensen study was a population-based study of all children born alive in Denmark from 1996 to 2006. National registers were used to identify children born to mothers exposed to valproate during pregnancy and diagnosed with autism spectrum disorders (childhood autism [autistic disorder], Asperger syndrome, atypical autism, and other or unspecified pervasive developmental disorders). Data were analysed by Cox regression adjusting for potential confounders (maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity). Children were followed up from birth until the day of autism spectrum disorder diagnosis, death, emigration, or 31 December 2010, whichever came first.

Results

Of 655,615 children born from 1996 through 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The mean age of the children at end of follow-up was 8.84 years (range, 4-14; median, 8.85). The estimated absolute risk after 14 years of follow-up was 1.53% (95% CI, 1.47%- 1.58%) for autism spectrum disorder and 0.48% (95% CI, 0.46%-0.51%) for childhood autism.

Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI, 2.59%-7.46%) for autism spectrum disorder (adjusted HR vs. non-valproate exposed women, 2.9 [95% CI, 1.7-4.9]) and an absolute risk of 2.50% (95% CI, 1.30%-4.81%) for childhood autism (adjusted HR, 5.2 [95% CI, 2.7-10.0]).

⁴⁹ Cohen MJ et al. Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. *Epilepsy Behav.* 2011 Oct; 22(2): 240-6.

⁵⁰ Akinbami et al. Attention Deficit Hyperactivity Disorder among children aged 5–17 years in the United States, 1998–2009. *NCHS Data Brief.* 2011;(70):1-8.

When restricting the cohort to the 6,584 children born to women with epilepsy, the absolute risk of autism spectrum disorder among 432 children born to mothers exposed to valproate during pregnancy was 4.15% (95% CI, 2.20%-7.81%) (adjusted HR, 1.7 [95% CI, 0.9-3.2]), and the absolute risk of childhood autism was 2.95% (95% CI, 1.42%-6.11%) (adjusted HR, 2.9 [95% CI, 1.4-6.0]).

There was very limited power to examine the risks associated with valproate use in women without a diagnosis of epilepsy.

The authors concluded that maternal use of valproate during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for maternal epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

The PRAC noted that diagnoses of childhood autism and autistic spectrum disorders were not blinded to valproate exposure which may have led to bias. Further to this, while there was considerable adjusting for potential confounders including parental psychiatric history, the study was not able to adjust specifically for parental autism which is one of the major variables associated with childhood risk. Adjustment for other key potential confounders including alcohol use, use of folate, and seizures during pregnancy was also not possible. However, higher risks of autism spectrum disorder and childhood autism were also found among children of women who used valproate during pregnancy compared to women who were previous users of valproate but who had stopped at least 30 days before conception. Risks were similar for children exposed to higher and lower doses of valproate however the study was not able to adjust for cumulative dose or changes in dose and it should be noted that the risks for both groups were still significantly greater than for non-valproate exposed women.

Impact of breast milk exposure

The available published pharmacokinetic data indicates that the transfer of valproate in milk is low. It is estimated that 1-10% total maternal serum levels might be transferred but this would vary depending on timing after dosing, the total daily dose, the volume and regularity of feeding and other maternal factors that could influence the transfer of drug to milk.

A recent publication by Meador et al. (2014)⁵¹ reported on an analysis of 181 breastfed children at age 6 who had been exposed in utero to antiepileptics. The results showed a higher IQ (by 4 points) and enhanced verbal abilities (by 4 points) in breastfed children compared to non-breastfed children, even after adjustment for other factors related to child cognitive outcomes (e.g. maternal IQ).

This study found no adverse cognitive effects of breastfeeding during maternal antiepileptic exposure or specifically valproate therapy.

There is currently limited data on the effects of breastfeeding during maternal antiepileptic drugs exposure. Although the study suggests that exposure during breastfeeding is not additionally harmful the limitations are acknowledged. There was a high level of missing data and no details on the frequency of breastfeeding, relationship of feed timing to antiepileptic drugs dose taken, or antiepileptic drugs blood levels in the child were available. In addition, this study only examined the effect of breastfeeding in children already exposed to antiepileptic drugs in utero and not in those previously unexposed. Finally, as only cognitive measures have been analysed, other effects of breastfeeding when patients are exposed to valproate or other antiepileptic drugs cannot be ruled out.

⁵¹ Meador KJ et al; for the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group. Breastfeeding in Children of Women Taking Antiepileptic Drugs: Cognitive Outcomes at Age 6 Years. JAMA Pediatr. 2014 Jun 16. doi: 10.1001/jamapediatrics.2014.118.

Effect of folic acid supplementation in the prevention of valproate related neural tube defects and developmental disorders

In the general population, folic acid supplementation during pregnancy has been demonstrated to reduce the frequency of neural tube defects. It is recommended that women with epilepsy contemplating pregnancy take supplemental folic acid.

Women should start taking folic acid at the recommended dosing before conception and continue taking until at least the end of the first trimester⁵².

The study by Jentink et al. (2010) has shown that folic acid supplementation reduces the risk of *spina bifida* in pregnancies unexposed to antiepileptic drugs⁵³. In this study, the group of women taking folic acid supplementation was defined as using at least 0.4 mg folic acid from 4 weeks before conception until 8 weeks in pregnancy.

However, there are no data showing that folic acid supplementation reduces the risk of birth defects or malformations for pregnancies exposed to valproate whatever the dose of folic acid administered⁵⁴.

In addition, there are no data available on the effect of folic acid on the reduction of risk of developmental disorders.

2.2.2.2. Spontaneous cases

A search of all unsolicited and serious related solicited cases reported after exposure in utero to valproate and its pro-drug valpromide was performed by one MAH. The cases were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A total of 2958 cases of exposure in utero with valproate and valpromide were retrieved from the database including 19 cases of paternal exposure reported as pregnancy exposure.

The majority of the cases arose from the use of valproate in the indication of epilepsy (53.1% (1570/2958)) followed by 5.5% (162/2958) of cases in bipolar disorder. For the migraine indication, 5 cases were reported. The indication was unknown in 39% of the remaining cases.

The MAH highlighted that 424 cases were reported in both sub-groups 'Congenital familial and genetic disorders' and 'Impaired cognitive development'. However, only 14% of the cases described coexisting diseases that could have confounded the impaired cognitive development (61/424). These conditions were mainly structural brain disease and deafness.

Congenital anomaly cases

A total of 1750 cases of congenital malformation out of the 2958 cases of exposure in utero with valproate and valpromide were identified in the MAH's pharmacovigilance database. Of these cases of congenital malformation, the main indications were epilepsy in 58% and unknown in 39% of cases.

The cases were mainly distributed in the following secondary System Organ Class (SOCs):

- Musculoskeletal and connective tissue disorders (675/1750, 39% of all cases) with the most frequently reported Preferred Terms (PTs) related to dysmorphism, polydactyly/arachnodactyly/brachydactyly/syndactyly/macrodactyly, limb/hand/foot

⁵² Crawford P et al. Best practice guidelines for the management of women with epilepsy. *Seizure*. 1999; 8, 201-217

⁵³ Jentink J et al. Does folic acid use decrease the risk for spina bifida after in utero.

exposure to valproic acid. *Pharmacoepidemiol Drug Saf*. 2010 Aug;19(8):803-7. doi: 10.1002/pds.1975.

⁵⁴ Morrow JI et al. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry*. 2009 May;80(5):506-11.

malformation, microcephaly/macrocephaly/brachycephaly/scaphocephaly/plagiocephaly.

- Nervous system disorders (621/1750, 36% of all cases) – the most frequently reported PT was 'spina bifida'.
- Cardiac disorders (414/1750, 23% of all cases) – the most frequently reported PTs related to atrial/ventricular septal defect, congenital heart disease NOS and congenital cardiovascular anomaly NOS.
- Pregnancy, puerperium and perinatal conditions (398/1750, 23% of all cases) – the most frequently reported PTs related to foetal anticonvulsant syndrome.

The MAH reported that the period of exposure during pregnancy was unknown for the majority of cases (1217/1750, 70% of all cases). Across all indications, 30% (518/1750) of cases were treated with valproate/valpromide during at least the first trimester of pregnancy. One fifth of all cases (21%, 359/1750) involved exposure during the entire pregnancy. Of patients with epilepsy, 32% (328/1017) received treatment during the entire pregnancy.

The daily dose was unknown in the majority of cases (59%, 1023/1750). When reported, patients were most frequently prescribed 1000-1500mg/day (33% of cases with dose reported, 243/727), or 700-1000mg/day (32%, 231/727). Only 4% of patients received >2500mg/day (29/727).

It is to be noted that the current product information of valproate and related substances recommends a maximum daily dose of 2500mg/day and states that most patients achieve seizure control with a daily dose of 1000-2000mg/day.

Impaired cognitive development cases

A total of 699 cases of impaired cognitive development out of the 2958 cases of exposure in utero with valproate and valpromide were identified in the MAH's pharmacovigilance database. Most cases were reported in the sub-groups 'Developmental delay' (586/699 i.e. 83.8%), 'Cognitive disorders' (153/699 i.e. 21.9%), 'Autism' (106/699 i.e. 15.2%) and 'Hyperactivity' (40/699 i.e. 5.7%). Dyspraxia was reported in 9 cases. Several cases may be involved in 2 or more sub-groups.

Regarding cases of impaired cognitive development, 6 cases were associated with a fatal outcome; however, all were confounded by severe congenital malformations.

ADHD and motor developmental delay cases

The MAH also performed a cumulative database review and a brief review of the literature to identify the association between in utero valproate exposure and a diagnosis of ADHD and delayed motor developmental milestones.

Twenty one (21) cases were reported with a diagnosis of ADHD after in utero exposure to valproate. In 17 out of these 21 cases, a congenital anomaly was also reported.

Most cases of ADHD were reported in children whose parents had been treated with monotherapy with valproate and/or valpromide (17/21 i.e. 81%).

A total of 132 cases of motor developmental delay after in utero exposure to valproate were also identified. In 105 out of these 132 cases, a congenital anomaly was also reported, mostly brain disorders, skeletal or limb anomalies and tube neural anomalies.

Most cases of motor developmental delay were reported in children born to patients treated in monotherapy with valproate and/or valpromide (107/132, i.e. 81%).

Intelligence quotient (IQ) cases

IQ information was reported in only a small proportion of the total number of cases of impaired cognitive development (69 cases for children out of 699, 10%).

Mental retardation was reported in four cases (reported IQ range 37-60) and in five cases reported IQ ranged from 70-77. In one case a normal IQ was observed and in two cases an IQ of above average (111-120) was reported. In one case the child had a performance IQ of 141 (gifted) and a verbal IQ of 88 (below average). In two cases severe mental retardations was reported. In the remaining cases, memory problems, adaptive behaviour deficit, motor skills deficit, autism spectrum disorders / Asperger syndrome, lower verbal IQ, or speech and language delay were reported.

In addition, a recent publication describes 45 cases (Baker and Bromley, 2011)⁵⁵, where children born to patients treated with valproate had a reduction in full scale IQ, described as a reduction in verbal IQ and a reduction in speed of processing.

Impact of breast milk exposure

The review of the pharmacovigilance database has identified a limited number of cases (n=2) of impaired cognitive development after exposure to valproate during breast feeding. In both cases, the patients were also exposed to valproate in utero.

Folic acid

The review of the pharmacovigilance database has identified a total of 537 cases reporting a diagnosis of neural tube defect (30.7%), among the 1750 cases of congenital malformations retrieved after in utero exposure to valproate,

Among the 537 cases reporting a diagnosis of neural tube defect after in utero exposure to valproate and valpromide, folic acid was supplemented in 9.7% (52/537) versus 90.3% (485/537) without reported folic acid supplementation.

The results showed that twice as many cases of neural tube defects ((33.3% [485/1455]) were reported without folic acid supplementation compared to cases of tube neural defects with folic acid supplementation (17.6% [52/295]). However, this result must be interpreted with caution due to the important number of cases without information provided on the concomitant drugs (included in the group without folic acid supplementation).

2.2.2.3. Conclusions on safety

The PRAC reviewed all available data from pre-clinical studies, pharmacoepidemiological studies, published literature and, spontaneous reports, as well as considering the views of patients, healthcare professionals and other relevant experts (i.e. in neurology, psychiatry, child neuropsychiatry, obstetrics etc.) on the safety of valproate and related substances in pregnant women and women of childbearing potential (for more detail on the individual groups consulted, see below sections 2.3, 2.4 and 2.5).

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). This is a greater risk of major

⁵⁵ Baker GA, Bromley RL. School-aged children who were exposed to sodium valproate in utero have impaired language score when compared with a population mean score. *Evid. Based Med.* 2011; 16(6): 178-9.

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 also 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.

Spontaneous cases of congenital malformations were also reported and the majority were reported in women treated for epilepsy.

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.

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. 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 IQ.

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).

Data on the impact of breast milk exposure with valproate are very limited. However, there is some evidence of no additional harm of valproate exposure through breast milk on the development of the child. The PRAC agreed that women should be informed of the data available and helped by healthcare professionals to make an informed decision whether to discontinue breast-feeding taking into account the benefit of breast feeding for the child.

Folic acid supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

2.2.3. Efficacy

Valproate in the treatment of generalised and focal epilepsy in pregnant women and women of childbearing potential

Epilepsy is a serious condition and seizures can have profound effects on maternal health, occasionally including maternal mortality. Moreover, frequent generalised tonic clonic seizures during pregnancy have been associated with poorer postnatal cognitive development of the child (Battino, 2013⁵⁶).

Valproate is considered to be an effective drug in the treatment of epilepsy. It is classified as probably efficacious/effective in the treatment of partial onset seizures (Level B) and possibly efficacious/effective in the treatment of generalised onset tonic-clonic seizures (Level C) by the International League Against Epilepsy (ILAE)⁵⁷.

The efficacy of valproate was not studied in the specific population of pregnant women as this population was excluded from clinical trials due to known risk of teratogenicity.

For the management of generalised epilepsy, valproate can be the only therapeutic option for some patients including pregnant women or women of childbearing potential, for whom other treatments have failed.

There is a lack of data on whether there is a specific group of women of child bearing potential who can only tolerate valproate for the management of focal epilepsy. The risks to pregnancy of focal seizures are considered to be less than that for generalised seizures. However, patients with focal epilepsy might develop generalised epilepsy over time and therefore valproate treatment may be warranted in these patients.

The PRAC noted a number of guidelines providing information relating to precautions for use of valproate in pregnancy:

The 2012 NICE guideline on epilepsy advises to *'be aware of teratogenic risk of valproate'* and to *'discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of antiepileptic drugs causing malformations and possible neurodevelopmental impairments in an unborn child'* (Recommendation 207). In addition, it is stated *"Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalised tonic-clonic seizures) but consider the risk of adverse effects of antiepileptic drugs and use the lowest effective dose of each antiepileptic drug, avoiding poly-therapy if possible (Recommendation 209)"*.

The American Academy of Neurology (AAN) and the American Epilepsy Society (AES) recommends to minimise intra-uterine exposure to anti-epileptic drugs, particularly poly-therapy and valproate.

Valproate in the treatment of manic episodes in bipolar disorder in pregnant women and women of childbearing potential

Bipolar disorder is a complex condition of major health relevance and chronic course with a lifetime prevalence of 1-2.4% and important rates of disability and poor quality of life, for which treatment

⁵⁶ Battino D et al.; EURAP Study Group. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Epilepsia*. 2013 Sep; 54 (9): 1621-7. Epub 2013 Jul 12.

⁵⁷ Glauser T et al.; ILAE Subcommittee on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013 Mar; 54 (3): 551-63. Epub 2013 Jan 25.

needs to be considered separately through the course of the illness for manic/ hypomanic, mixed and depressive episodes, and long-term treatment^{58,59,60}.

Valproate is effective in the management of acute mania and for those patients who benefit in the acute phase sodium valproate is indicated for maintenance therapy.

There are no data directly evaluating the efficacy of valproate treatment in pregnant women or women of childbearing potential. There are also no data assessing the percentage of patients suffering from manic episodes and/or continuation of treatment after the manic episodes that show exclusively a full clinical response under valproate.

Some bipolar patients have been found to be intolerant, unresponsive, or both, to alternative mood stabilising treatments including lithium, other anti-epileptics or neuroleptics. These patients may become pregnant while successfully stabilised using valproate. Discontinuation of valproate in these patients may induce a recurrence of a mood episode i.e. depression, manic episode or mixed episode that are generally known to respond to emergency treatment only after a considerable time-lapse.

Such persistent mood episodes during pregnancy, induced by cessation of valproate, may harm the intra-uterine offspring due to behavioural disorders including insufficient intake and dehydration, excessive use of drugs or alcohol, exhaustion due to sleep disturbance or hyperactivity.

These risks, and the risks associated with mood stabilising treatment, were quantified in a recent study by Boden et al. (2012)⁶¹, who concluded that: "Bipolar disorder in women during pregnancy, whether treated or not, was associated with increased risks of adverse pregnancy outcomes".

The PRAC noted a number of guidelines providing information relating to precautions for the use of valproate in pregnancy in this indication.

Several guidelines on bipolar disorders mention that valproate should be avoided for treatment of bipolar disorder in women of childbearing potential, women planning pregnancy and pregnant women, unless clearly necessary^{62,63,64}.

Valproate in the prophylaxis of migraine in pregnant women and women of childbearing potential

There are only limited data on the efficacy of valproate in the management of migraine prophylaxis in women of childbearing potential. There are sufficient therapeutic alternatives that can be used to treat acute migraine attacks. Valproate should not be used as daily prophylactic medication in pregnancy or in women of childbearing potential or pregnancy who are not using effective methods of contraception.

⁵⁸ Nivoli AM et al. New treatment guidelines for acute bipolar mania: a critical review. *J Affect Disord.* 2012 Oct; 140 (2): 125-41. Epub 2011 Nov 17.

⁵⁹ Nivoli AM et al. New treatment guidelines for acute bipolar depression: a systematic review. *J Affect Disord.* 2011 Mar; 129 (1-3): 14-26. Epub 2010 Jun 9.

⁶⁰ Grunze H et al; WFSBP Task

Force on Treatment Guidelines for Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry.* 2013 Apr; 14 (3): 154-219.

⁶¹ Boden R et al. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. *BMJ*2012; 345:e7085.

⁶² Llorca PM et al. Dépistage et prise en charge du trouble bipolaire: Résultats. *L'Encéphale* 2010; 36(4):S86-S102.

⁶³ Yatham LN et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disorders* 2013; 15: 1–44.

⁶⁴ The diagnosis and management of the epilepsies in adults and children in primary and secondary care. National Institute for Health and Clinical Excellence. 2012.

Conclusion

For the epilepsy and manic episodes in bipolar disorder indications, the PRAC concluded that in view of the risks associated with use during pregnancy, 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.

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. Pregnancy must be excluded before start of treatment with valproate.

2.3. Consultation of patients' organisations and valproate patients, families and carers

On 27 June 2014, a meeting involving representatives from patients' organisations in epilepsy, bipolar disorder and migraine and patients from organisations representing the patients, families and carers who have been affected by valproate was convened. The aim being to achieve an exchange of information with a focus on understanding the patients' perspective on the communication, awareness and understanding of the risks of valproate during pregnancy and in women of childbearing potential and to explore their views on options for improving communication of risk.

Overall, patients were concerned about the level of information provided by healthcare professionals about the potential effects of valproate and related substances when used during pregnancy. They considered the information provided limited and inconsistent across the countries represented at the meeting and across different products (e.g. reference and generics).

The participants agreed that targeted and appropriate information to healthcare professionals and patients was key and that measures should be put in place in this respect. In addition, the general view of the participants was that the information given to patients and parents should be harmonised at European level and should be the same in terms of risks regardless of the age of the patient, should be provided from the first prescription, and should be written in an age appropriate language.

The participants of the meeting considered that different communication tools can be used to deliver this information to the patient, such as package leaflet, a patient booklet with additional information on the risks. All participants proposed that a written statement highlighting the risks should be signed off by the female patients at different milestones of their life.

The PRAC took into account the views of the participants in its final recommendation, in particular with regard to improving the risk communication to patients and healthcare professionals.

2.4. Consultation of healthcare professional organisations

The PRAC also obtained additional information from the healthcare professionals' perspective on the communication, awareness and understanding of the risk of valproate during pregnancy and in women of childbearing potential.

Most of the healthcare professional organisations consulted replied that it is current clinical practice to inform women of child bearing potential and pregnant women who have been or will be prescribed with valproate about the risk of congenital malformations and risk of developmental disorders.

They also provided their opinions on the appropriate person to discuss with patients at different stages of treatment and/or patient follow-up, such as the general practitioner, neurologist, gynaecologist, obstetrician, epilepsy nurses, pharmacists, or family planning specialist.

Proposals for additional communications tools and measures to help increase the awareness and the understanding of women regarding the risk of valproate during pregnancy were also provided.

The views and proposals from healthcare professional organisations were also taken into account by the PRAC in its final recommendation.

2.5. Consultation of the Scientific advisory group in Neurology issues

On 3 October 2014, a Scientific Advisory Group (SAG) on neurology including relevant experts (i.e. experts in neurology, psychiatry, child neuropsychiatry, obstetrics etc.) was convened to gain insight on the use of valproate and related substances in clinical practice in females (including children), women of childbearing potential and pregnant women in the treatment of epilepsy, migraine disorders and prophylaxis of migraine attacks.

Based on clinical experience, the SAG acknowledged that in epilepsy (generalised and focal) valproate might be used in women and adolescents with childbearing potential when other appropriately chosen and applied therapies used at effective dosage are ineffective or not tolerated. In such cases patients should use effective contraception during treatment.

For manic episodes in bipolar disorder and continuation of the treatment after stabilisation, valproate might be used in women and adolescents with childbearing potential when other therapies are ineffective or not tolerated. Again, in such cases patients should use effective contraception during treatment.

If valproate is used for the prophylaxis of migraine attacks, the SAG supports a contraindication of valproate in pregnant women and women of childbearing potential not using an effective method of contraception.

As a general strategy and based on the identified risks for the offspring, the SAG considered that all efforts should be made in order to avoid the use of valproate in women and adolescents of child bearing potential unless other therapeutic options are impossible. Such strategy should also be considered in female children, as the discontinuation of an efficacious treatment with valproate may be extremely difficult when the childbearing age is reached, and the recommendation to children of appropriate contraception in the future does not seem suitable or effective.

They also considered that a thorough discussion between the patient and a qualified specialist is needed to assess the risk to the potential pregnancy against the risk of relapse or recurrence of symptoms occurring because of a possible withdrawal or change to another medication.

The SAG agreed that the risk of congenital malformation and cognitive disturbances is clearly identified and the presented data can be considered robust. The risk is higher than for other anti-epileptics and mood stabilizers. There is no safe dosage that could be identified.

With regard to the developmental disorders (ASD, ADHD and related disorders), the SAG considered that the available data appear less robust than those related to birth defect and cognitive delay.

The role of folic acid in the risk of reduction of all congenital malformations, including developmental disorders was also discussed. The SAG considered that there was no clear evidence that the use of the recommended dose of 0.4 to 0.8 mg/day at least one month before getting pregnant and during pregnancy brings about an added benefit (different to the one valid for the general population) in cases

where treatment with valproate is applied. On the other hand, the use of high dosage up to 5mg/day is not supported by data. Nevertheless, the SAG considers that the absence of evidence showing any efficacy of folic acid supplementation to prevent the additional risks linked to valproate use does not go against the usual recommendation to supplement valproate treated women as general population with a 0.4 mg/day dose, or with a 4 mg/day dose when women have already had a neural tube defects affected pregnancy.

The SAG also commented on appropriate post-natal follow-up of children exposed to valproate in-utero and considered that the specialist and/ or general health care worker monitoring the child (as per the applicable national prevention programme) should be informed about the treatment with valproate applied to the mother during pregnancy. The specialist's attention should be directed to systematically evaluate such children for behavioural and cognitive disturbances.

2.6. Risk minimisation activities

In view of the above, the PRAC recommended amendments to the product information (see section 2.7) and communication to healthcare professionals through a direct healthcare professional communication (DHPC – see section 4). In addition, the PRAC recommended the following additional risk minimisation activities:

Information and awareness of Healthcare professionals and patients

Education measures are necessary 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.

The PRAC recommends that a single version of the educational materials is disseminated, where appropriate. The MAHs are encouraged to collaborate and liaise with the NCA to facilitate the dissemination of the agreed educational material.

- A guide for prescribers

The PRAC recommended the development of a guide for prescribers to make sure that valproate prescribers are aware of the risks associated with the use of this product in female children, women of childbearing potential and pregnant women and that the patients are also informed about these risks, as appropriate. This guide should allow prescribers to familiarise themselves with the latest data on disorders of development in the exposed child that can be seriously debilitating. In addition, the guide should familiarise the prescribers with key actions to mitigate the risks associated with the use of valproate in exposed girls and women by using the patient booklet and the acknowledgment of risk information form.

The guide for prescribers should be used by the prescribers in conjunction with the Summary of Product Characteristics.

The core elements of the said guide for prescribers are attached to this report.

- A patient booklet

The PRAC recommended that a booklet for women who are being prescribed valproate and are able to get pregnant (of child-bearing age) is developed. The booklet should provide information on risks to the unborn child due to in-utero exposure to valproate and related substances. In order to provide adequate information, it should be tailored for different situations in the life time of a woman: the first prescription, women continuing valproate treatment and not trying to have a child, women of

childbearing potential continuing valproate treatment and considering trying to have a child, pregnant women (unplanned pregnancy) whilst continuing valproate treatment.

The patient booklet should be used in conjunction with the package leaflet.

The core elements of the said patient booklet are attached to this report.

- Acknowledgment of risk information form including a checklist for prescribers and a checklist for patient or carer

The PRAC recommended that an acknowledgment of risk information form is developed. This form should include a checklist for prescribers and patients or carers. This checklist is intended to be used by physicians experienced in the management of epilepsy and/or bipolar disorder and migraine (where this indication is approved) to initiate a discussion with girls and women patients and/or their carers about the suitability of a treatment with a valproate and its risks. The document should be signed by both the prescriber and the woman patient or carer.

The checklist should be used in conjunction with the Summary of Product Characteristics and Package Leaflet.

The core elements of the said acknowledgment of risk information are attached to this report.

Case-control study

The possibilities to further elucidate the potential risks of in utero exposure for attention deficit hyperactivity disorder (ADHD) was discussed, e.g. through a case-control study. It was also noted that such study should not be limited to valproate use only, but should ideally assess all antiepileptic drugs.

Imposed mandatory additional pharmacovigilance activity (key to benefit-risk balance):

The PRAC recommends that the MAHs conduct a drug utilisation study to assess the effectiveness of the proposed risk minimisation measures and to further characterise the prescribing patterns for valproate. The study design should aim to evaluate and quantify the effectiveness of the risk minimisation measures, and should include a pre- and post-implementation analysis and assessment. The MAHs are highly encouraged to collaborate in conducting this study.

In accordance also with the Article 23 of Regulation (EC) No 726/2004 the products will be included in the list of products for additional monitoring. The black symbol with the corresponding explanatory statement will be included in the product information of the products.

2.7. Product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risks associated with valproate use during pregnancy. These changes include amendments to sections 4.2, 4.3, 4.4, 4.6 and 4.8 of the Summary of Product Characteristics (SmPC).

The SmPC should reflect that for female children, women of childbearing potential and pregnant women, valproate treatment should be initiated and supervised by a specialist in the management of epilepsy or bipolar disorder. It should also reflect that valproate should not be used in female children, women of childbearing potential and pregnant women unless other treatments are ineffective or not tolerated. The need for treatment should be regularly reviewed. In addition, these products should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged released formulation. The daily dose should be divided into at least two single doses.

In those marketing authorisations where the prophylaxis of migraine attacks is authorised, the PRAC considered 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. Pregnancy must be excluded before start of treatment with valproate.

In addition, wherever the migraine indication is approved, the treatment should only be initiated and supervised by a specialist experienced in the management of migraine.

Further information concerning developmental disorders in children exposed in-utero to valproate was also included. In addition, a black box was included in order to further highlight the risks and precaution of valproate use in pregnancy and women of childbearing potential.

The corresponding sections of the package leaflet were amended accordingly.

3. Overall discussion and benefit/risk assessment

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). 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.

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. 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 IQ.

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).

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, 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 alternatives 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.

Furthermore, the possibilities to further elucidate the potential risks of in utero exposure for attention deficit hyperactivity disorder (ADHD) was discussed, e.g. through a case-control study. It was also noted that such a study should not be limited to valproate use only, but should ideally assess all antiepileptic drugs.

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.

4. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to raise awareness of the new recommendations in the product information and other risk minimisation measures. The specialists targeted are neurologists, psychiatrists, general practitioners, obstetricians/gynaecologists, family planning centres, pharmacists, health visitors, midwife, and school nurses. The communication is to be sent in accordance with the agreed communication plan. The final version of this DHPC agreed by the PRAC is provided together with the communication plan.

All concerned MAHs in each Member State are encouraged to liaise with national competent authorities to collaborate in order to prepare and circulate a single DHPC in each Member State, where appropriate. The letter should cover all valproate containing products authorised in that Member State and therefore all indications authorised.

5. Conclusion and grounds for the recommendation

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 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.