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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Medicinal products containing substances related to valproate

Active substance: sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium

Procedure number: EMEA/H/A-31/1454

Note:

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



Table of contents

1. Information on the procedure	3
2. Scientific discussion	3
2.1. Background information on the procedure	3
2.2. Introduction.....	5
2.3. Risk of congenital malformation in the offspring in subsequent pregnancies.....	6
2.4. Risk of congenital malformation in offspring following exposure due to paternal use or transgenerational exposure to valproate	9
2.5. Clinical aspects	24
2.5.1. Data on efficacy	24
2.5.2. Data on safety	26
2.5.3. Switch or discontinuation of treatment	40
2.5.4. Analysis of data on visual reminder on the outer packaging	42
3. Expert consultation and Stakeholders input	44
3.1. Written consultations	44
3.2. Public hearing	45
3.3. Healthcare professionals, patients' organisations and patients, families and carers meeting	46
3.4. Scientific advisory group on Neurology.....	48
3.5. Scientific advisory group on Psychiatry.....	49
3.6. Working group on Quality review of documents (QRD)	50
4. Risk management.....	50
4.1. Risk management plan.....	50
4.2. Pharmacovigilance activities	50
4.2.1. Non-clinical studies	50
4.2.2. Non-interventional clinical studies.....	51
4.3. Risk minimisation measures.....	51
4.3.1. Amendments to the product information.....	51
4.3.2. Educational materials.....	53
4.3.3. Direct Healthcare Professional Communication and Communication plan	56
4.3.4. Improved distribution of educational materials and additional channels of communication	56
4.3.5. Pack size and original packaging.....	57
4.3.6. Additional monitoring	58
5. Conclusions and Benefit-risk balance	58
6. Conditions to the marketing authorisations.....	62
7. Grounds for Recommendation	64
Appendix 1	67
Divergent position(s).....	67

1. Information on the procedure

On 08 March 2017 France triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the risk minimisation measures in the current pregnancy exposure of the treatment with medicinal products containing substances related to valproate and their impact on the benefit-risk balance of and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure includes all formulations and related pharmaceutical forms. The injectable formulations (solutions for injection or infusion) which are used under emergency circumstances are part of this review.

Further to the assessment of the available data resulting from pharmacovigilance activities, the PRAC issued on 08 February 2018 a recommendation to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

2. Scientific discussion

2.1. Background information on the procedure

In October 2014, PRAC concluded a review¹ (EMA/H/A-31/1387) under Article 31 of Directive 2001/8/EC of all available data from non-clinical, clinical and 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. The review confirmed the already known teratogenic risks associated with the use of valproate in pregnant women. Data derived from a meta-analysis (Meador et al, 2008)² (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, where 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 anti-epileptics drugs (AEDs).

Available data showed an increased incidence of both minor and major malformations in children born to mothers treated with valproate and related substances during pregnancy. The most common types of malformations included 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 also shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of exposed children. This risk seems also to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period at 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

¹ Valproate referral 2014
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f)

² Meador K, Reynolds MW, Crean S 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

abilities, poor language skills (speaking and understanding) and memory problems (Meador et al, 2008)³, (Meador et al 2009)⁴, (Bromley et al, 2008)⁵, (Cummings et al, 2011)⁶.

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 the ones of 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 (Meador et al, 2013)⁷. 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).

Based on this review the PRAC recommended in 2014 the restrictions on the use of valproate containing substances due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

Changes to product information for valproate and related substances were that:

- for the treatment of epilepsy, it should not be used in female children, women of childbearing potential (WCBP) and pregnant women unless alternative treatments are ineffective or not tolerated;
- for the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated.

For epilepsy and bipolar disorders, women for whom valproate is the only option after trying other treatments should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

Regarding the management of migraine prophylaxis in WCBP, the PRAC noted that there are only limited data on the efficacy of valproate. As 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 WCBP who are not using effective methods of contraception. The PRAC therefore concluded that in the prophylaxis of migraine attacks valproate should be contraindicated in pregnancy or in WCBP who are not using effective methods of contraception.

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 were agreed, as well as recommendation for educational materials to be developed.

Finally, the Marketing Authorisation Holders (MAHs) of valproate and related substances were requested to perform a drug utilisation study (DUS) to assess the effectiveness of the recommended risk minimisation measures and to further characterise the prescribing patterns for valproate with a

³ Meador K, Reynolds MW, Crean S, *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.

⁴ Meador KJ, Penovich P, Baker GA, *et al.* Antiepileptic drug use in women of childbearing age. *Epilepsy Behav* 2009 Jul;15(3): 339-43.

⁵ Bromley RL, Mawer G, Clayton-Smith J, *et al.* Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 2008;71(23):1923-4.

⁶ Cummings C, Stewart M, Stevenson M, *et al.* Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011 July;96(7):643-7.

⁷ Meador KJ, Baker GA, Browning N, *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.

pre- and post-implementation analysis and assessment, conducted in more than one Member State. The preliminary results of this DUS have been submitted to PRAC and are described further down in this report.

In addition to the European Union-level post-authorisation safety study (PASS) requested by the PRAC, France performed a national pharmacoepidemiological study programme covering all the indications of valproate products (based on data of French national medico-administrative databases), together with a national survey conducted in a sample of 222 pharmacies in April-June 2016.

The results of the study provide evidence that, despite the measures recommended further to the review in 2014, a high level of exposure to sodium divalproate and valpromide (substances related to valproate) among women of childbearing potential persisted in the recent period in France. Indeed, 27,707 women aged 15-49 years had at least one reimbursement for these products during the first trimester of 2016. The results showed also that among pregnant women, sodium divalproate and valpromide (bipolar disorder indication only) are generally stopped early during the course of pregnancy, i.e. during the first trimester: among women ever exposed during their pregnancy between 2007 and 2014, 94% had been exposed during the first trimester versus 15% during the second and 14% during the third trimester. This situation contrasts with that of valproic acid prescribed for epilepsy, for which exposure is largely maintained throughout pregnancy (85%, 68% and 66% exposed during the first, second and third trimester, respectively).

Finally, the results from the French survey conducted between April and June 2016 in community pharmacies showed that prescribing conditions were not adhered to, especially in bipolar disorder indication. Conditions regarding supply and use were adhered to in only 36% of dispensing among girls and women of childbearing potential (WCBP) who had been prescribed valproic acid (substance related to valproate) by a psychiatrist.

In view of the above, France triggered on 08 March 2017 a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2.2. Introduction

Valproate and related substances (valproic acid, sodium valproate, magnesium valproate, valproate semisodium and valpromide) are licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorders in Europe. Worldwide, these products are approved and marketed in more than 120 countries. Valproate and related substances have been authorised via national procedures in all EU Member States, and in Norway and Iceland.

In some EU Member States (MSs) valproate is also indicated in prophylaxis of migraine attacks.

In 2009, the bipolar disorders indication was restricted to the treatment of manic episode when lithium is contraindicated or not tolerated. Continuation of treatment after the manic episode can be considered in patients who have responded well to valproate.

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.

For the current review, the MAHs were requested to discuss the therapeutic value and the need for valproate among the currently available therapeutic options for all authorised indications with a focus

on use in WCBP and pregnant women. Patient populations that may only respond to valproate should be identified. Furthermore, they were requested to provide all data on the effectiveness of the risk minimisation measures implemented with the previous referral (e.g. compare the prescription of valproate before and after, as well as discuss the risk awareness and behaviour of HCPs and patients). The MAHs were also asked to discuss any other proposals for minimising the risks of valproate exposure in pregnancy and in WCBP.

2.3. Risk of congenital malformation in the offspring in subsequent pregnancies

Questions were raised on the risk of congenital malformation in the offspring in subsequent pregnancies.

In the general population, and in women with epilepsy, parental history of congenital malformation and history of malformation in siblings are known risk factors for the recurrence of congenital malformation in subsequent pregnancies. Studies evaluating the risk of recurrence of congenital malformation in siblings of children with congenital malformation exposed to valproate *in utero* are based on a very limited sample sizes (as low as 7 in 3 studies and 32 in the remaining one). These studies show inconsistent results in terms of the risk of recurrence. From these studies it is not possible to determine the contribution of an antiepileptic drug, or specifically valproate, above and beyond the contribution of other known risk factors for recurrence, i.e., parental history of congenital malformation or history of malformation in siblings.

A cumulative search from the first case entered in the global pharmacovigilance database on the originator (Sanofi) to 31 May 2017 was performed to identify all solicited and unsolicited cases of congenital malformation reported in siblings after *in utero* exposure to valproate as a suspect drug, using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0.

The search retrieved a total of 307 cases of congenital malformation reported in children belonging to the same family after *in utero* exposure to valproate, among a total of 2476 cases of congenital malformation.

Those 307 cases involved a total of 132 families.

In the majority of the 132 families (n=120), there were either 2 (98/132, i.e., 74.2%) or 3 (22/132, i.e., 16.7%) children reported with a congenital malformation. All siblings in these 132 families had *in utero* exposure to valproate. It is noteworthy that the number of cases was smaller than the number of impacted children because in 4 families, only 1 case was created for all children in each of these families.

The indication for valproate treatment was epilepsy in 93.2% (286/307) of cases. The indication for valproate therapy was unknown in the remaining cases.

Overall, the most frequently reported congenital malformations were dysmorphism (161/307, i.e., 52.4%), and foetal anticonvulsant syndrome ([FACS] 150/307, i.e., 48.9%), then multiple congenital abnormalities not otherwise specified ([NOS], 25/307, i.e., 8.1%), congenital hand malformation (23/307, i.e., 7.5%), congenital anomaly NOS (23/307, i.e., 7.5%) and congenital foot malformation (20/307, i.e., 6.5%).

Neural tube defects, referring to MedDRA PTs "Neural tube defect", "Spina bifida", "Spina bifida occulta" and "Spine malformation", were reported in 6.2% (19/307) of cases and cardiac malformations, referring to the MedDRA PTs "Atrial septal defect", "Cardiac septal defect", "Congenital cardiovascular anomaly", "Dextrocardia", "Heart disease congenital", "Pulmonary artery atresia",

“Transposition of the great vessels” and “Ventricular septal defect” were reported in 12.1% (37/307) of cases.

These data only do not allow the determination of the contribution of valproate to the risk of recurrence on top of known risk factors of congenital malformations such as parental history of congenital malformations and history of malformations in siblings.

In 109 out of the 132 families affected, at least one “similar” congenital malformation, common to at least 2 siblings of the same family, was reported and the malformations reported in at least 5 cases were the following: foetal anticonvulsant syndrome (FACS) involving numerous and various malformations (n = 61 families), and other types of malformations outside a context of foetal anticonvulsant syndrome (FACS), i.e., dysmorphism/face malformation (n = 22), limb malformation (n = 7), neural tube defects (n = 6) and cardiovascular malformations (n = 6).

In 14 cases, the children had a parental history of congenital malformation and in 3 of these cases, a history of maternal alcohol intake, a known risk factor for congenital malformation, was also reported. In 10 cases, maternal alcohol intake was the only risk factor reported. The daily dose of valproate during pregnancy was not reported in 31.3% (96/307) of cases.

When the information on valproate daily dose was available, 39.3% (83/211) of cases were reported at a daily dose below or equal to 1 g; 65.9% (139/211) of cases were reported at a dose below or equal to the World Health Organization (WHO)-defined daily dose of 1.5 g; 8.5% (18/211) of cases were reported at a daily dose above 2 g.

Congenital malformations reported in siblings after *in utero* exposure to valproate occurred at all valproate doses, even at low doses. No clear dose-dependence has been shown, based on the available data.

Cases of interest by concomitant treatment

As already mentioned, the only reported indication of valproate for the cases of interest was epilepsy. Polytherapy is defined as the co-administration of antiepileptic drugs and/or benzodiazepines. It is noteworthy that when no information was provided on concomitant drugs, the cases were classified as “monotherapy”.

Most cases were reported in patients treated with valproate monotherapy (251/307, i.e., 81.8% vs. 56/307, i.e., 18.2% in polytherapy).

In 76/307 (24.8%) cases, genetic investigations were reported. In 72 cases, results were normal. In the other 4 cases, results were as follows:

Evidence of a shared chromosomal abnormality was discovered during a family genetic work-up, i.e., deletion of chromosome 7 in 2 siblings and the patients’ mother. Of note, the microdeletion of the long arm of chromosome 7 induces a deletion of the *CNTNAP2* gene, which is involved in both epilepsy and autism.

Genetic analysis revealed an inactivation profile of extremely deviated X chromosomes in a patient and in the patient's mother, with heterozygote deletion of more than 13 Mb of telomeric chromosomal region Xp22.33p22.2 and duplication of about 11 Mb of telomeric chromosomal region Xq27.3q28.

Supernumerary chromosome and duplication of chromosome NOS was noted in one patient. It is notable that in a family of three children with congenital malformations, a family history of fragile X syndrome was reported. In one of these patients, genetic investigations were normal; in the other two children, there was no information about additional genetic workup.

Review of published epidemiological data

A literature search was conducted in PubMed and EMBASE up to 30 June 2017 using the following search terms: "recurrence" OR "siblings" AND "congenital" OR "malformations" OR "pregnancies" AND "valproate" OR "antiepileptics".

In the general population, familial risk of recurrence of congenital malformation was evaluated in the Medical Birth Registry of Norway, where siblings of children with heart defects had a 3.6-fold increased risk of congenital heart defects compared with siblings of children without heart.

In 2 registries of children exposed to antiepileptic drugs *in utero*, parental history of congenital malformation was found to increase the risk of congenital malformations by 4.4-fold (European Registry of Antiepileptic Drugs and Pregnancy) and malformation in previous offspring by 3.4-fold (Australian Register of Antiepileptic Drugs in Pregnancy).

The risk of recurrence of malformations in subsequent pregnancies in women with epilepsy who had a malformation in a previous pregnancy has been studied in different pregnancy registries or cohorts: The UK Epilepsy and Pregnancy Register, the Australian Register of Antiepileptic Drugs in Pregnancy, the Medical Birth Registry of Norway, a prospective study in Japan, Italy and Canada and the Indian Kerala registry.

The results of the different studies including sample size, rate of congenital malformation after a first pregnancy wherein a baby was born with a congenital malformation and relative risks with 95% CIs are displayed in the table 1 below:

Author, year, registry	Number of pregnancies	Rate of malformations in subsequent pregnancies after malformations versus after normal outcome	Relative risk and 95%CI
Kaneko 1999 ⁸ , prospective study in Japan, Italy, and Canada	983 offspring, including 26 cases of malformation during a first pregnancy	All 26.9% vs. 9.5%	p = 0.011
Begum 2013 ⁹ Kerala Registry of Epilepsy and Pregnancy	246 women with at least two prospective pregnancies in which 21 cases of malformation presented during a first pregnancy 64 women treated with valproate in which 7 index pregnancies presented with cases of malformation	All 4.8% vs. 9.3% Valproate 0% (0/7) vs. 10.5%	0.49 [0.06–3.80] 0.90 [0.82–0.98]
Campbell 2013 ¹⁰ , UK Epilepsy and Pregnancy Registry	103 first pregnancies with cases of malformation (including 32 women treated with valproate) 563 normal first pregnancies (including 128 treated with valproate)	All AEDs 16.9% vs. 9.8% Valproate 21.9% (7/32) vs. 14.8%	1.73 [1.01–2.93] 1.47 [0.68–3.20]

⁸ Kaneko S, Battino D, Andermann E, Wada K, Kan R et al. Congenital malformations due to antiepileptic drugs. *Epilepsy Res.* 1999 Feb; 33(2-3): 145-58

⁹ Begum S, Sarma SP, Thomas SV. Malformation in index pregnancy in women with epilepsy is not followed by recurrence in subsequent pregnancy. *Epilepsia* 2013 Dec; 54(12):e163-7.

¹⁰ Campbell E, Devenney E, Morrow J, Russell A, Smithson WH et al. Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs *in utero*. *Epilepsia* 2013 Jan; 54(1):165-71.

Vajda 2013 ¹¹ , Australian Register of Antiepileptic Drugs in Pregnancy	84 first pregnancies with cases of malformation (including 44 in women treated with valproate) and 15 siblings (including 7 in women treated with valproate)	All AEDs 35.7% vs. 3.1% Valproate 57.2% (4/7) vs. 7.0%	17.6 [4.5–68.7] 17.8 [2.7–119.1]
Veiby 2014 ¹² , Medical Birth Registry of Norway	61 cases of malformation and 18 siblings (including 7 women treated with valproate)	All AEDs 22.2% vs. 6.7% Valproate 42.9% (3/7) vs. 6.7%	3.97 [1.30–12.1] 10.4 [2.3-46.7]

Overall, in the general population, and in women with epilepsy, parental history of congenital malformation and history of malformation in siblings are known risk factors for the recurrence of congenital malformation in subsequent pregnancies.

Studies evaluating the risk of recurrence of congenital malformation in siblings of children with congenital malformation exposed to valproate *in utero* are based on a very limited sample sizes (as low as 7 in 3 studies and 32 in the remaining one). These studies show inconsistent results in terms of the risk of recurrence. From these studies it is not possible to determine the contribution of an antiepileptic drug, or specifically valproate, above and beyond the contribution of other known risk factors for recurrence, i.e., parental history of congenital malformation or history of malformation in siblings.

Based on epidemiological data, parental history of congenital malformation and occurrence of malformation in a previous pregnancy are known risk factors for recurrent congenital malformation in future pregnancies in the general population and in women with epilepsy.

Four out of five publications provided data specifically on valproate. It is noted that the sample size of these studies was generally very low (three studies with 7 and one study with 32 siblings). Although the size of these studies was small to allow reliable comparisons, it is noted that in all studies, there was an increased recurrent risk of malformations seen for all antiepileptic medications. Finally, it is noted that one of the studies concluded that the siblings of children with congenital malformation exposed to valproate *in utero* had a lower risk of congenital malformations, as compared to siblings of children who did not have congenital malformations following *in utero* exposure to valproate.

In conclusion, currently available data do not indicate that valproate increases the risk of recurrent congenital malformations beyond the contribution of the genetic predisposition, parental history of malformations and its own teratogenic potential in an ongoing pregnancy.

2.4. Risk of congenital malformation in offspring following exposure due to paternal use or transgenerational exposure to valproate

Questions have been raised on the effect of valproate not only on the children exposed *in utero* to valproate but whether these effects can travel through the generations. This was also a question from stakeholders and especially patients during the public hearing (more details below in this report). The PRAC requested the MAHs to present the current evidence on this issue. A summary of the responses from one MAH is given here which also includes adverse events reporting in pharmacovigilance databases, but kept all together.

¹¹ Vajda FJ, O'Brien TJ, Lander CM, Graham J, Roten A et al. Teratogenesis in repeated pregnancies in antiepileptic drug-treated women. *Epilepsia*. 2013 Jan; 54(1):181-6.

¹² Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol*. 2014 Mar; 261(3):579-88.

Risk of congenital malformation in offspring following exposure due to paternal use of valproate

Spontaneous reports

A total of 38 cases involving children potentially exposed to valproate solely via the father have been retrieved. Overall, 14 cases of paternal exposure or potential exposure to valproate via the father and involving adverse reactions have been identified. Eleven cases were reported as serious. Three cases were reported by HCPs and 11 cases were reported by non-HCPs. The involved adverse drug reactions (ADRs) referred to induced abortion (n = 3), spontaneous abortion (n = 2), foetal anticonvulsant syndrome (n = 3), congenital hearing disorders NOS (n = 2), congenital tri-atrial heart (n = 1), congenital cataract (n = 1), congenital hydrocephalus (n = 1), learning disorder (n = 1).

Twenty four (24) cases of paternal exposure or potential exposure to valproate via the father did not report any ADRs but the pregnancy outcome was not reported in 19 cases. Five cases resulted in live births. All cases were assessed as non-serious. One case was solicited and the other 23 unsolicited cases were all reported by non-HCPs.

In all cases, valproate was administered to the father at least at time of the conception. It is noteworthy that no karyotype investigations were performed for any of these cases. No conclusions could be drawn based on these cases.

Published epidemiological data

Two relevant publications have been identified on epidemiological data.

In 2013, the impact of *in utero* exposure to antiepileptic drugs (AEDs) and child development at 18 and 36 months was investigated using data entered from mid-1999 to December 2008 in the prospective Norwegian Mother and Child Cohort study (MoBa) (Veiby et al, 2013)¹³.

A total of 363 children had a father with reported epilepsy, of which 37% were treated with an AED at any time during the 6 months preceding conception and were followed for at least 18 months. The study did not distinguish between the different AEDs, therefore, there were no specific results for valproate. However, children of fathers with epilepsy treated with an AED had a significantly greater risk of adverse development scores for tests of personal social skills [OR: 2.3, (95% Confidence Interval (CI): 1.3 to 4.1)] and a measure of autistic traits [OR: 3.7 (95% CI: 1.4 to 10.1)] at 18 months of age compared with children whose fathers had epilepsy, but were untreated. No differences in gross or fine motor skills were observed between groups. No statistically significant increase in risk was found for any of the outcomes measured at 36 months. The authors consider that this study did not provide evidence of a causal association between paternal exposure to AEDs and adverse child development in children with fathers who have epilepsy.

In 2013, Engeland and colleagues¹⁴ performed a cohort study that linked two population-based registries, the Medical Birth Registry of Norway and the Norwegian Prescription Database. The study cohort consisted of 340,000 pregnancies from 2004 to 2010. The study did not identify paternal drug exposure as an important risk factor for adverse pregnancy outcomes, and importantly, did not report

¹³ Veiby G, Daltveit AK, Schjølberg S, Stoltenberg C, Øyen AS, Vollset SE, et al. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia* 2013 Aug; 54(8): 1462-72.

¹⁴ Engeland A, Børge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, Furu K. Effects of preconceptional paternal drug exposure on birth outcomes: cohort study of 340_000 pregnancies using Norwegian population-based databases. *Br J Clin Pharmacol*. 2013, Apr; 75(4):1134-41.

any increased risk of adverse outcomes after paternal use of AEDs. Of note, 347 cases of fathers taking valproate during the observation period were included in the analysis.

No increased risks could after paternal exposure to valproate be identified from these two published observational studies.

Exposure via seminal fluid

Valproate could be transmitted via the seminal fluid of patients treated with valproate, either by direct *in utero* exposure (e.g., during fertilization or embryonic development) or by maternal systemic exposure via the vaginal route.

Valproate transfer into seminal fluid was investigated (Swanson et al, 1978)¹⁵. In this study, one subject was administered single, oral 500 mg valproate doses on four separate occasions, with at least one week between successive doses and a second subject was administered one single, oral 500 mg valproate dose. Valproate was then quantified in seminal fluid and plasma over time using a gas– liquid chromatographic assay. Following single oral 500 mg doses of valproate, valproate concentrations in semen were low compared with concentrations in concurrent plasma samples. The semen: plasma drug concentration ratio for both subjects ranged from 0.058 to 0.091. Therefore, valproate transfer into seminal fluid was minimal under these conditions. The highest valproate concentration determined in semen was 3.26 µg/mL at 4.3 hours after dosing (range for both subjects: 0.53 to 3.26 µg/mL).

Valproate vaginal dose and systemic exposure, when a male partner is exposed to valproate, can be estimated (Banholzer et al, 2012)¹⁶, by including several conservative assumptions:

Seminal fluid volume is 6 mL; vaginal absorption is 100%; and Pharmacokinetic linearity, i.e. a direct linear relationship between dose and systemic exposure.

Using the highest valproate concentration in seminal fluid (Swanson et al, 1978)¹⁶ (3.26 µg/mL), a vaginal (or *in utero*) dose of valproate can be calculated as: 3.26 µg/mL x 6 mL seminal fluid = 19.56 µg.

Following a single, oral 500 mg valproate dose, systemic exposure (area under the curve) in women was reported to be 917.9 mg.h/L (Ibarra et al, 2013)¹⁷. As the oral bioavailability of valproate is considered to be 100% (Gugler et al, 1980)¹⁸, a direct correlation can be made between valproate oral and vaginal administration, resulting in a projected AUC of 0.0367 mg.h/L following a vaginal dose of 19.56 µg.

Using the data reported (Swanson et al, 1978)¹⁶ and assumptions (Banholzer et al, 2012)¹⁷ in combination with the pharmacokinetic characteristics of valproate, the estimated systemic exposure to valproate via the vaginal route when a male partner is exposed to valproate is estimated to be approximately 25 000-fold less than that of a single 500 mg oral dose in women. It is noted that male patients would be receiving valproate as a multiple-dose treatment regimen, and systemic exposure at steady-state would be higher than that following a single 500 mg dose used for the above exercise; however, the same principles would apply although absolute concentrations would probably be higher.

In conclusion, there are very limited available data on the transmission of valproate via seminal fluid. The above exercise has attempted to use these data from only one male subject to estimate direct

¹⁵ Swanson BN, Harland RC, Dickinson RG, Gerber N. Excretion of valproic acid into semen of rabbits and man. *Epilepsia*. 1978 Dec; 19(6):541-6

¹⁶ Banholzer ML, Buergin H, Wandel C, Schmitt G, Gocke E, Peck R, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partners. *J Transl Med*. 2012 Jun 21; 10: 129.

¹⁷ Ibarra M, Vázquez M, Fagiolino P, Derendorf H. Sex related differences on valproic acid pharmacokinetics after oral single dose. *J Pharmacokinetic Pharmacodyn*. 2013 Aug; 40(4): 479-86.

¹⁸ Gugler R, von Unruh GE. Clinical pharmacokinetics of valproic acid. *Clin Pharmacokinetic*. 1980 Jan-Feb; 5(1): 67-83.

in utero exposure and maternal systemic exposure. As a proportion of dose, the amount of valproate present in the semen appears to be very low ($\leq 10\%$). When considering direct *in utero* exposure, e.g., during fertilization or embryonic development, thresholds for toxic effects are unknown. However, effects from maternal systemic exposure can probably be considered negligible.

The MAH provides an estimation of AUC for valproate in a woman following exposure to valproate via seminal fluid. This AUC was estimated as 0.0367 mg.h/L based on a highest measured concentration in semen of one of two male subjects following a single oral dose of 500 mg (3.26 $\mu\text{g/mL}$). AUC in women following a single oral dose of 500 mg was reported to be 917.9 mg.h/L. The PRAC agreed that exposure to valproate via seminal fluid is significantly lower (i.e. 25,000 times) than following direct treatment of pregnant women and unlikely to cause adverse effects by itself.

Genetic mechanism

Genetic damage, if any, induced in the germ cell deoxyribonucleic acid (DNA) of male patients exposed to valproate could potentially be transmitted as mutations to their offspring. Hereafter, data on the genotoxicity of valproate collated from in-house data and the peer-reviewed scientific literature are presented in the table 2 below.

Table 2 - Genotoxicity: Animal and *in vitro* data

Assay type	Test system	Doses	Duration of treatment	Results	Reference
<i>In vitro</i> bacterial reverse mutation (Ames test)	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	0.001-5 $\mu\text{L/plate}$	NA	Non mutagenic	[Proprietary Information]
<i>In vitro</i> bacterial reverse mutation (Ames test)	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	0.01, 0.1 and 1 mg/plate	NA	Non mutagenic	[Proprietary Information]
<i>In vitro</i> DNA repair	Primary cultures of rat hepatocytes (Fisher 344)	0.1, 1, 10 and 100 $\mu\text{g/mL}$	18-20 hours	No induction of DNA repair	[Proprietary Information]
<i>In vivo</i> chromosome aberration test	Rat (Sprague-Dawley and Long Evans) bone marrow 5 rats per group	65, 150 and 350 mg/kg (oral) Doses previously used in rat teratology study	5 days	No induction of chromosome damage	[Proprietary Information]
<i>In vivo</i> dominant lethal test	Mouse ICR 10 mice per group	65, 150 and 350 mg/kg (oral) Doses previously used in mouse teratology study	5 days	No change in rate of resorptions and implantations	[Proprietary Information]

<i>In vivo</i> Micronucleus test	Mouse BALB/c (Dams & pups; mothers & newborns) Peripheral blood	100 mg/kg (Intraperit oneal) NA	3 days G12– 14 of gestation	Increased incidence of micronucleated erythrocytes	Fucic et al, (2010) ¹⁹
<i>In vivo</i> micronucleus test	Mouse (Swiss albino) young (24–28 days) and adult males Rat (Sprague- Dawley) young (21– 24 days) and adult males Peripheral blood	500 mg/kg (Intraperit oneal)	3 days	Increased incidence of micronucleated erythrocytes in young mice treated with VPA alone. In young and adult rats and mice, 3-day pretreatment with VPA enhanced the genotoxic effects of cyclophosphamide, methotrexate and zidovudine.	Ahmad et al, (2013) ²⁰
<i>In vivo</i> chromosome aberration test	Mouse (Swiss albino) males Bone marrow	100 mg/kg (Intraperit oneal)	21 days	Increased incidence of chromosome aberration. Reduction of incidence by vitamin E.	Abdella et al, (2014) ²¹
<i>In vivo</i> DNA strand breaks (Comet assay)	Mouse (Swiss albino) Sperm	100, 200 and 400 mg/kg (Intraperit oneal)	28 days	Increased DNA damage at 400 mg/kg Associated with decrease in sperm count, decrease in testis and epididymis weight, sperm head abnormalities, oxidative stress and 8-oxo-2'- deoxyguanosine.	Khan et al (2011) ²²

Most of the studies that aimed to evaluate the potential ability of valproate to induce genetic damage were conducted in somatic cells. Only limited information was generated using male germ cells. However, results obtained in somatic cells can generally be extrapolated to germ cells.

Genetic toxicology studies were conducted by MAHs for valproate between 1977 and 1988. All studies were negative and no genotoxic potential for valproate was identified. However, as these studies were conducted more than 25 years ago, it should be noted that they were not performed in accordance with today's standards (i.e., Organization for Economic Co-operation and Development test guidelines for genotoxicity and November 2011 ICH S2 guideline), neither in terms of the battery of tests

¹⁹ Fucic A, Stojković R, Miškov S, Zeljezic D, Markovic D, Gjergja R, et al. Transplacental genotoxicity of antiepileptic drugs: animal model and pilot study on mother/newborn cohort. *Reprod Toxicol.* 2010 Dec; 30(4):613-8.

²⁰ Ahmad T, Shekh K, Khan S, Vikram A, Yadav L, Parekh CV, et al. Pre-treatment with valproic acid, a histone deacetylase inhibitor, enhances the sensitivity of the peripheral blood micronucleus assay in rodents. *Mutat Res.* 2013 Feb 18; 751(1):19-26.

²¹ Abdella EM, Galaly SR, Mohammed HM, Khadrawy SM. Protective role of vitamin E against valproic acid-induced genotoxicity and hepatotoxicity in mice. *The Journal of Basic & Applied Zoology.* 2014; 676:127-39

²² Khan S, Ahmad T, Parekh CV, Trivedi PP, Kushwaha S, Jena G. Investigation on sodium valproate induced germ cell damage, oxidative stress and genotoxicity in male Swiss mice. *Reprod Toxicol.* 2011 Dec; 32(4):385-94.

performed nor in terms of experimental conditions. This in-house package of studies consisted of two *in vitro* assays, a reverse gene mutation test in bacteria (Ames test) and an *in vitro* DNA repair test in rat hepatocytes, and two *in vivo* assays, a chromosome aberration test in rat bone marrow and a mouse dominant lethal test that evaluates resorptions and impact on implantations resulting from genetic damage in male germ cells. For both *in vivo* studies the animals received 65, 150 and 350 mg/kg for five days (i.e., the doses used in teratology studies where teratogenic effects were observed).

For complementary information, two carcinogenicity studies were conducted in-house in mouse and rat models in 1979. The rat study showed no tumour findings. The mouse study was negative despite some findings in the liver and lungs of male mice. This conclusion is supported by the comparable tumour incidence after exposure to valproate versus the background incidence in this strain of mouse, as described in the Registry of Industrial Toxicology Animal-data (RITA) database. Therefore, carcinogenicity data derived from these models is considered to reinforce the lack of genotoxic potential for valproate.

Some evidence of an increased incidence of DNA and chromosome damage (chromosomal aberrations or micronuclei) has been reported in rodents after exposure to valproate. For example, an increased incidence of micronucleated reticulocytes was reported in mouse peripheral blood from mothers and newborns after intraperitoneal injection of 100 mg/kg valproate on gestational days 12 to 14 (Fucic et al, 2010)²⁰, and in young mice after administering 500 mg/kg for 3 days (Ahmad et al, 2013)²¹. An increased frequency of cells with chromosomal aberrations was observed in mouse bone marrow tissue after administering valproate 100 mg/kg for 3 weeks (Abdella et al, 2014)²². A Comet assay showed DNA strand breaks in sperm associated with sperm-head abnormalities and oxidative stress in mice treated with valproate 400 mg/kg for 28 days (Khan et al, 2011)²³. Those DNA and chromosomal findings were reported as most probably resulting from indirect mechanisms (i.e., not a direct interaction between valproate and DNA), such as DNA damage resulting from oxidative stress and inhibition of histone deacetylases (HDACs). One of the consequences of inhibiting HDAC is to increase chromatin decondensation, resulting in chromatin instability, enhanced sensitivity to DNA nucleases, and increased access of DNA to macromolecules and genotoxins (xenobiotics, such as intercalating agents, anticancer drugs, DNA reactive oxidative species from exogenous and/or origin, etc.). It has also been shown to be responsible for DNA damage and apoptosis (Marchion et al, 2005)²³. Exposure to valproate was demonstrated to be associated with an increase in the formation of 8-oxo-2'-deoxyguanosine (8-oxo-dG), which is used as a biomarker of radical oxygen species (Khan et al, 2011)²³. Moreover, a reduced genotoxic effect of valproate in rodents was observed when it was co-administered with vitamin E (antioxidant) (Abdella et al, 2014)²². Pre-treatment with valproate was shown to increase the detection of other genotoxins (e.g., sensitivity to anticancer drugs), most probably due to DNA decondensation and increased access to DNA (Ahmad et al, 2013)²¹. This HDAC-inhibiting property of valproate has been envisaged for cancer therapy (Biswas et al, 2017)²⁴.

The overview shows that tests for gene mutations were negative and that tests for clastogenicity (i.e. potential for giving rise or inducing disruption or breakages of chromosomes) were (partly) positive. It was suggested that clastogenic findings could be due to indirect mechanisms such as oxidative stress and inhibition of histone deacetylases (HDACs). It was not further discussed which types of DNA damage caused by valproate could be transmitted to the offspring. It seems likely that gene mutations in sperm cells could be transmitted to the offspring. Tests for gene mutations were however negative, implying that this type of transmission is not likely to occur. Clastogenicity in the form of severe chromosome damage is expected to lead merely to death of sperm cells / reduced fertility and not to

²³ Marchion DC, Bicaku E, Daud AI, Sullivan DM, Munster PN. Valproic acid alters chromatin structure by regulation of chromatin modulation proteins. *Cancer Res.* 2005 May 1;65(9):3815-22.

²⁴ Biswas S, Rao CM. Epigenetics in cancer: Fundamentals and Beyond. *Pharmacol Ther.* 2017 May;173:118-134.

transmission of mutations to the offspring. It is unknown whether sperm cells with slight chromosomal damage could still be used to fertilize an ovum and lead to a viable zygote, which would thus contain genetic changes, and this was not further discussed.

Some evidence of an increased incidence of chromosome damage (sister-chromatid exchange -SCE, chromosomal aberrations or micronuclei) has been observed in patients exposed to valproate versus healthy controls. However, these data may have been impacted by confounding factors, and conflicting results have been reported when patients treated with valproate are compared with untreated patients.

For example, a slight increase in the incidence of both SCE and chromosomal aberrations were observed in 20 children with epilepsy treated with valproate for 6 to 52 months compared with healthy matched control children, but also when children with epilepsy treated with valproate were compared with other children with epilepsy who were not treated with valproate, and when children with epilepsy were used as their own controls prior to initiating treatment (i.e., 10 children with epilepsy before and after they took sodium valproate for 6 to 7 months) (Hu et al, 1990)²⁵. In contrast, while an increased incidence of SCE was reported in lymphocytes derived from patients treated with valproate compared with healthy controls, no increase in SCE was noted in lymphocytes of patients (n = 20) treated with valproate monotherapy for more than 6 months compared with patients who had not yet received therapy, except indigenous Indian remedies (Taneja et al, 1992)²⁶.

It is noted that inconsistent results have been published in literature regarding patients with epilepsy treated with valproate compared with untreated patients with epilepsy. Based on this no conclusions can be drawn. The PRAC recommended more research on this issue.

Epigenetic changes induced in male germ cells, if any, have been suggested as a potential mechanism of transmitting abnormalities to the offspring.

Epigenetic changes consist in three main components: histone modification, DNA methylation and non-coding ribonucleic acid (RNA), resulting in modified gene activity and expression without modifying nuclear DNA sequences, unlike genetic mutations (Simmons et al, 2008)²⁷.

The epigenetic properties of valproate, via inhibition of HDAC class I and IIa, were first described in early the 2000s (Phiels et al, 2001²⁸; Kubota et al, 2012²⁹; Houtepen et al, 2006³⁰; Hrabeta et al, 2014³¹; Dickinson et al, 2010³²).

HDAC is a histone modifying enzyme that participates in the remodelling of chromatin and as a consequence regulation of DNA methylation and gene expression (Trerotola et al, 2015)³³. The histone acetylation and deacetylation of lysine on histone tails are directly coupled to “on” and “off” states of gene transcription and regulation (Allis et al, 2016)³⁴.

²⁵ Hu LJ, Lu XF, Lu BQ, Huang YQ. The effect of valproic acid on SCE and chromosome aberrations in epileptic children. *Mutat Res.* 1990 Jan;243(1):63-6.

²⁶ Taneja N, Kucheria K, Jain S, Tandon JK, Maheshwari MC. Sister-chromatid exchanges are increased in epileptics, but not by sodium valproate. *Mutat Res.* 1992 Dec;283(4):233-5.

²⁷ Simmons D. Epigenetic influence and disease. *Nature Education.* 2008;1(1):6

²⁸ Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem.* 2001 Sep 28;276(39):36734-41.

²⁹ Kubota T, Miyake K, Hirasawa T. Epigenetic understanding of gene-environment interactions in psychiatric disorders: a new concept of clinical genetics. *Clin Epigenetics.* 2012 Jan 20;4(1):1.

³⁰ Houtepen LC, van Bergen AH, Vinkers CH, Boks MP. DNA methylation signatures of mood stabilizers and antipsychotics in bipolar disorder. *Epigenomics.* 2016 Feb;8(2):197-208.

³¹ Hrabeta J, Stiborova M, Adam V, Kizek R, Eckschlager T. Histone deacetylase inhibitors in cancer therapy. A review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2014 Jun;158(2):161-9.

³² Dickinson M, Johnstone RW, Prince HM. Histone deacetylase inhibitors: potential targets responsible for their anti-cancer effect. *Invest New Drugs.* 2010 Dec;28 Suppl 1:S3-20.

³³ Trerotola M, Relli V, Simeone P, Alberti S. Epigenetic inheritance and the missing heritability. *Hum Genomics.* 2015 Jul 28;9:17.

³⁴ Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet.* 2016 Aug;17(8):487-500.

Only a limited number of studies exploring the possible transmission of HDAC inhibitor-induced epigenetic changes via father to offspring were identified; most of the published studies referred to *in utero* exposure. No valproate-specific data were found.

Jia and colleagues (2015)³⁵ reported that HDACi 4b, a HDAC1/3-targeting inhibitor, may persistently alter paternally-inherited gene expression. In this study, the authors found that inhibiting HDAC alters the expression of several DNA methylation-related genes, potentially inducing DNA methylation changes on a genome-wide scale. The authors demonstrated that inhibiting HDAC1/3 can elicit changes in the expression of genes related to DNA methylation in mouse brain and cause selected alterations in CpG methylation in DNA from control and HD human fibroblasts. Moreover, Huntington's Disease (HD) transgenic offspring of HDACi 4b-treated male HD transgenic mice exhibited improved disease phenotypes compared with HD transgenic offspring from vehicle-treated mice. The behavioural differences were sexually dimorphic, with males showing more pronounced improvements compared with females. This effect is consistent with the high proportion of Y chromosome-linked genes exhibiting differential methylation in response to HDACi 4b. This study also demonstrated transgenerational effects via paternal transmission, and the authors suggested that HDAC inhibitors may induce germ-line epigenetic modifications, such as alterations in the sperm DNA methylome, and become permanently programmed to be similar to the DNA methylation of an imprinted gene. According to the authors, these findings will have significant implications for human health because they enforce the concept that ancestral drug exposure may be a major molecular factor that can affect disease phenotypes, arguably in a positive manner.

In conclusion, epigenetic changes induced in male germ cells have been suggested as a potential mechanism of transmitting abnormalities to the offspring, for instance by modifying gene expression. A potential route of changing gene expression is inhibition of HDAC, which is involved in remodelling of chromatin and regulation of DNA methylation. Publications suggest that valproate is capable of inducing altered DNA methylation (Houtepen et al, 2016)³¹, by acting as a HDAC inhibitor (Phiel et al, 2001²⁹; Kubota et al, 2012³⁰). Jia and colleagues (2015)³⁶ describe an experiment in which it was shown that a change in gene expression in male mice after exposure to a HDAC inhibitor was observed also in the offspring of these mice. DNA methylation is an epigenetic modification that can be inherited in the germ line and epigenetic transgenerational inheritance of altered phenotypes has been observed in many species including humans. Phiel and colleagues (2001)²⁹ suggested that teratogenicity of valproate may be associated with HDAC inhibition. In experiments in *Xenopus* embryos they found that valproate and a well characterized HDAC inhibitor (trichostatin A) were teratogenic, whereas non-teratogenic analogues of valproate also did not inhibit HDAC. Based on this information, it can be concluded that the possibility of valproate inducing changes in the offspring by inducing transgenerational changes in gene expression, is worth investigating further. The PRAC recommended more research on this issue.

Regarding testing for direct genotoxicity, it should be carefully considered whether repeating existing tests will be useful. For instance, two *in vivo* micronucleus tests were already performed and conducting another one is not expected to add relevant information. Instead, it is recommended to focus on the difference between gene mutations and clastogenicity. Current data suggest that valproate may not be able to cause transmission of gene mutations to the offspring, because both Ames tests were negative. Performing an *in vitro* mouse lymphoma assay may be useful to confirm this, because this test gives an indication for the occurrence of both gene mutations and clastogenicity.

³⁵ Jia H, Morris CD, Williams RM, Loring JF, Thomas EA. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. Proc Natl Acad Sci U S A. 2015 Jan 6; 112(1):E56-64.

Further, it would be relevant to know whether sperm cells with slight forms of chromosomal damage could still fertilize an ovum and produce a viable embryo.

The weighted cumulative evidence is insufficient at this stage to support or rule out a causal association between valproate and reported observations in children exposed to valproate via their father.

Further studies with tests of genotoxicity according to ICH S2(R1) to confirm the absence of direct genotoxicity or *as per* ICH S2, i.e. *in vitro* Ames test and *in vivo* combined Micronucleus and Comet Assays in relevant tissues should be conducted, to explore the potential impact of valproate on the sperm epigenome, and its potential consequences for offspring.

The feasibility of conducting a retrospective study using existing Real World data sources, in order to evaluate whether paternal exposure to valproate at the time of conception is associated with an increased risk of Autism Spectrum Disorders (ASD) in offspring, is being investigated in European countries.

Therefore, it is proposed to perform a retrospective study to evaluate the possible association between paternal exposure to valproate and the risk of congenital abnormalities and neurodevelopmental disorders including autism spectrum disorders in offspring. It is also recommended that additional non-clinical studies need to be performed to evaluate the possible impact of valproate on genome and epigenome of germ cells (*i.e.* mutagenicity, clastogenicity and gene expression).

Risk of congenital malformation in third generation offspring

Post-marketing spontaneous reports

In total 41 cases related to exposure to valproate via father or grandparents and damage in the unborn child have been retrieved from the MAH's pharmacovigilance database. Of these 41 cases, 14 cases were serious and 27 were non-serious cases reported without any ADR.

Of the 14 serious cases, 11 involved exposure to valproate via father, 2 involved *in utero* exposure to valproate and one involved exposure to valproate via grandparents.

Two serious cases (siblings), which occurred in France, reported exposure to valproate during their mothers pregnancy, 'exposure via father', and autism and facial dysmorphism. Their father and mother were treated with valproate for epilepsy. A third serious case was reported which involved potential exposure to valproate via grandparents and referred to autism. His father was treated with valproate for epilepsy and his mother, who did not have epilepsy, was exposed to valproate sodium *in utero*. The child's mother is reported as having presented with foetal valproate syndrome. No details regarding the mother's foetal valproate syndrome, or further relevant data, are available.

All 3 cases were not medically confirmed and contained limited information. No conclusions could be made regarding the effects of valproate on children via "exposure from father" based on these cases, involving also *in utero* exposure or grand-parents exposure to valproate.

A total of six cases of abnormalities in children born to a third generation after valproate exposure, i.e., involving exposure to valproate via grand-mothers, have been identified in a cumulative search to 31 July 2017 in the global pharmacovigilance database. In five cases, exposure to valproate during pregnancy was ascertained based on the narratives and in the last case, the grandmother was treated with valproate sodium with no mention of the precise dates.

All these six cases were serious. Three of them were reported by HCPs and three by non-HCPs. In five cases, valproate was administered as monotherapy, or it was unknown if concomitant drugs were

administered. In the sixth case, valproate was co-administered with carbamazepine and phenobarbital. It is noteworthy that no karyotype investigations were performed for any of these cases.

No epidemiological studies describing potential risks associated with valproate exposure in the third generation have been identified.

Non-clinical data

Two potential mechanisms have been considered to discuss effects in third-generation offspring, genetic changes induced by valproate in germ cells that would be transmitted to foetus up to the third generation; and/or epigenetic changes induced by valproate in germ cells that would be transmitted to foetus up to the third generation.

Theoretically if genetic (DNA) damage could be induced in F1 germ cells (embryos treated *in utero*), resulting mutations could be transmitted to the third generation.

The PRAC considers that further evaluation of the genetic mechanisms for potential transmission via male or even female germ cells need to be explored.

With regards the epigenetic transgenerational inheritance there is evidence that environmental factors can induce epigenetic alterations in the germ cells that can potentially be transmitted trans-generationally (Hanson et al, 2016; ³⁶ Pembrey et al, 2014 ³⁷). This non genetic form of inheritance operates during specific critical windows of exposure that are linked to the developmental biology of germ cells (sperm and eggs). Three essential stages have been identified (Holland et al, 2013)³⁸ ; (i) establishment of a signal triggered within the germline; (ii) the mature gamete transmits the signal through fertilization; and (iii) the signal influences genome function in the developing offspring, to confer an altered developmental outcome.

Exposure must occur very early in embryogenesis for any modification to the mammalian germline epigenome to remain stable.

Chromatin-associated marks, such as DNA methylation and histone modifications that are transmitted in mature gametes may alter developmental outcomes via various pathways post-fertilization and during cell differentiation in a largely lineage-specific manner, making the understanding of the molecular processes quite complex.

As summarised by Wang and colleagues (2017)³⁹ epigenetic information undergoes extensive reprogramming during different stages of male and female germ cell development, such as during embryogenesis and early postnatal life. Epigenetic regulation, including DNA methylation, 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) and histone modifications, such as H3K9me2, H3K9ac, and H3K27me3 at certain genes, as well as RNA granules, such as processing bodies (P-bodies), mediate dynamic epigenetic changes. DNA methylation is largely eliminated from the genome of female and male germlines during gametogenesis and post-fertilization, seemingly diminishing the possibility of replicative inheritance.

In mammals, the epigenetic information that is conserved during the two major waves of epigenetic reprogramming occurring after fertilization and during sperm development in the germline are

³⁶ Hanson MA, Skinner MK. Developmental origins of epigenetic transgenerational inheritance. *Environ Epigenet.* 2016;2(1).

³⁷ Pembrey M, Saffery R, Bygren LO; Network in Epigenetic Epidemiology; Network in Epigenetic Epidemiology. Human transgenerational responses to early-life experience: potential impact on development, health and biomedical research. *J Med Genet.* 2014 Sep;51(9):563-72.

³⁸ Holland ML, Rakyan VK. Transgenerational inheritance of non-genetically determined phenotypes. *Biochem Soc Trans.* 2013 Jun;41(3):769-76.

³⁹ Wang Y, Liu H, Sun Z. Lamarck rises from his grave: parental environment-induced epigenetic inheritance in model organisms and humans. *Biol Rev Camb Philos Soc.* 2017 Nov;92(4):2084-111.

inherited and represent a plausible mechanism of transmitting environmental information across generations. Recent data suggest that histone modifications have the ability, alongside DNA methylation, to serve as a mediator of epigenetic memory from one generation to the next in many organisms.

Parental environments also exert gender/sex-specific effects on their progeny, in a similar manner to which gender differences are observed in most communicable diseases, including psychiatric and neurological disorders. Differences in epigenetic plasticity during gamete maturation can potentially contribute to gender-specific epigenetic inheritance (Wang et al, 2017)⁴⁰.

Inheritance is generally investigated in a three-generation paradigm involving an *in utero* environmental insult to the F1 mid-gestation when the primordial germ cells that form the second generation are being specified. Phenotypic outcomes are often observed in the F3 after transmission via the male germline in each generation. Germline-specific DNA methylation and other chromatin marks also occur, resulting in the induction of a germ-cell-specific transcriptional programme. Environmental perturbation of any of these processes may result in altered chromatin states that could potentially be transmitted with the mature gamete, if not removed later in germline development. There is some evidence to suggest that early maternal exposure during gestation can confer phenotypic changes to the exposed offspring, as well as to their offspring. Moreover, it should be noted that differentiating between gestational/maternal effects and germline transmission in female-inherited traits is inherently challenging. Therefore, key aspects of non-genetic gametic inheritance in mammals are often limited to exploring evidence of paternal inheritance (Holland et al, 2013)³⁹.

The exposure of F0 generation (pregnant female) directly exposes her, the F1 generation foetus, and the F2 generation germ-line within the F1 generation foetus through multi- or intergenerational transmission (Hanson et al, 2016)³⁷. Therefore, when a pregnant female is exposed to a challenge, the F3 generation is the first generation that is truly a test of transgenerational inheritance transmitted through the germ line in the absence of direct exposure; outcomes in the F0, F1, and F2 generations being due to multigenerational exposure. If an adult male or non-pregnant female is exposed, the F0 generation adult and germ line will generate the F1 generation through multigenerational transmission, so it is the F2 generation (grand offspring) that the first recipients of transgenerational inheritance in this instance. In all cases in the third generation, none of the offspring cells have been directly exposed to valproate and any transmission must have occurred via germ-lines (Hanson et al, 2016)³⁷.

In utero exposure of animal models to valproate has been reported to provoke neurodevelopmental and autism-like disorders, in 2000's and 2010's respectively (Ergaz et al, 2016⁴⁰; Ranger et al, 2016⁴¹). In rodents, valproate was found to disrupt postnatal neurogenesis (apoptotic neurodegeneration) and induce autism-like behaviours following single or repeated exposure during different phases of brain development. Some of these studies showed that histone modifications may play an important role in neurodevelopmental diseases (Abel et al 2008)⁴² and embryogenesis, e.g. increased histone acetylation found in the neuroepithelium, heart, and somites in mice exposed to valproate *in utero* (Tung et al, 2010)⁴³.

However, limited animal data on transgenerational inheritance of valproate-induced phenotypes have been communicated in the scientific literature.

⁴⁰ Ergaz Z, Weinstein-Fudim L, Ornoy A. Genetic and non-genetic animal models for autism spectrum disorders (ASD). *Reprod Toxicol*. 2016 Sep;64:116-40.

⁴¹ Ranger P, Ellenbroek BA. Perinatal Influences of Valproate on Brain and Behaviour: An Animal Model for Autism. *Curr Top Behav Neurosci*. 2016;29:363-86.

⁴² Abel T, Zukin RS. Epigenetic targets of HDAC inhibition in neurodegenerative and psychiatric disorders. *Curr Opin Pharmacol*. 2008 Feb;8(1):57-64.

⁴³ Tung EW, Winn LM. Epigenetic modifications in valproic acid-induced teratogenesis. *Toxicol Appl Pharmacol*. 2010 Nov 1;248(3):201-9.

Only one publication was identified (Choi et al, 2016)⁴⁴, which suggested that ASD-like phenotypes induced by a single exposure to valproate (300 mg/kg) on Day 10 *in utero* could be transmitted epigenetically via a paternal line in mice up to third generation. In this study, dams (F0 females) were exposed to valproate 300 mg/kg on gestational day 10 and F1 male offspring exposed to valproate *in utero* were mated with naïve females to produce the second generation (F2), and then similarly mated the F2 to deliver the third generation (F3). The males of first generation (F1) valproate-exposed offspring exhibited ASD-like phenotypes (increased seizure susceptibility, hyperactivity, decreased anxiety, impaired sociability and imbalanced expressions of excitatory/inhibitory synaptic markers in frontal cortices); phenotypes were consistent with the previous data published by the authors on valproate-induced ASD in animals. The ASD phenotypes found in F1 were also observed in F2 and F3 offspring, suggesting a multi- and trans-generational epigenetic inheritance of the ASD-like phenotypes.

This result was considered to be hypothesis-generating regarding the epigenetic mechanisms having a role in the potential transgenerational transmission of autism. However, the clinical relevance of this study remains unclear, in the absence of clinical evidence demonstrating transgenerational inheritance of abnormal phenotypes and behaviours following valproate exposure in patients. While the results of this study encourage the investigation of epigenetic transgenerational inheritance of ASD in humans, the authors acknowledged that identifying patients with ASD and no evident genetic aetiology and tracking the transgenerational transfer of abnormal behaviours across at least three generations is unlikely to be feasible.

Furthermore, phenotypic transmission of ASD was presented as a surrogate marker for germline epigenetic transmission that has yet to be confirmed. New genomic technologies are enabling epigenetic mechanisms, such as histone modification and DNA methylation, and their influence on gene expression and transcription to be investigated across generations. However, while these techniques may be used in future research to identify potential epigenetic effects of valproate exposure, isolating a valproate epigenetic signal may be difficult given the inherent environmental influences on epigenetics that are difficult to control for.

In conclusion, this is the first publication reporting multi-(up to F2 generation) and transgenerational (F3 generation) ASD inheritance after rodent *in utero* exposure to valproate. Relevance of these preliminary findings in animals and their potential extrapolation to humans would require complementary investigations on additional autism spectrum disorder-specific parameters, and underlying genetic and/or epigenetic mechanisms.

Considering the amount of literature on epigenetic transgenerational transmission of effects induced by diverse environmental factors, it cannot be excluded that this is also possible after exposure to valproate. Choi and colleagues (2016)⁴⁵ observed transgenerational transmission (to F3 offspring) of autism-like symptoms and increased expression of excitatory postsynaptic proteins in mice. A symptom of teratogenicity was also observed in the F1 offspring (crooked tail, considered a mild form of neural tube defect) but not in the F2 and F3 offspring. Although the number of animals was rather low (6 dams per group) and only one dose was used and the functional consequences of the effect on the proteins were not clear. Overall, the amount of tests performed and the consistency of effects up to the F3 generation suggest that there was some transgenerational effect of valproate on the investigated autism-like symptoms and proteins. According to the authors, the absence of malformed tails in the F2 and F3 generations suggests that teratogenicity induced by valproate is mediated by a mechanism other than transmissible epigenetic changes. However, this single observation is not

⁴⁴ Choi CS, Gonzales EL, Kim KC, Yang SM, Kim JW, Mabunga DF, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. *Sci Rep.* 2016 Nov 7;6:36250

sufficient to conclude that epigenetic changes are not involved in teratogenicity. As mentioned, Phiel and colleagues (2001)²⁹ associated teratogenicity of valproate with HDAC inhibition.

Having assessed all available non-clinical data, the PRAC concluded that the cumulative evidence is insufficient to support a causal association between valproate and reported observations in third generation of children born to parents exposed to valproate. More research is necessary to discover whether valproate indeed may induce transgenerational adverse effects to the offspring and which types of effects.

Having assessed all available data, the PRAC concluded that the cumulative evidence is insufficient to support a causal association between valproate and reported observations in third generation of children born to parents exposed to valproate and that the possibility of valproate inducing changes in the offspring by inducing transgenerational changes in gene expression should be further investigated.

Effects on mitochondrial genes and function and their implications for health

Mitochondria are organelles surrounded by two membranes that have their own genome. The main function of mitochondria is to act as the power plants of eukaryotic cells by performing cellular respiration. Mitochondria are supplied with nutrients by the cell, which it metabolizes and turns into energy. To evaluate the effects of valproate on mitochondrial genes and function, and their potential implications on an individual's health, pharmacovigilance textbooks and the scientific literature were searched for relevant information.

Accumulation of micro vesicular lipid droplets between myofibrils adjacent to mitochondria was found in muscle biopsies from seven children taking valproate (Meyler's, 2015)⁴⁵. Ultrastructural abnormalities in the mitochondria suggested that these could have resulted from impaired mitochondrial fatty acid oxidation.

As detailed by Labbe and colleagues (2008)⁴⁶, potential action of drugs on mitochondria is an important point to be taken into account, in particular during the development of new drugs. Several *in vitro* and *in vivo* investigations can be performed to determine if newly developed drugs disturb mitochondrial fatty acid oxidation (FAO) and the oxidative phosphorylation process, deplete hepatic mitochondrial DNA (mtDNA), or trigger the opening of the mitochondrial permeability transition (MPT) pore. As drugs can be deleterious to hepatic mitochondria in some individuals but not in others, it may also be important to use novel animal models with underlying mitochondrial and/or metabolic abnormalities.

Being a simple natural fatty acid, valproate is a substrate for the FAO pathway, which primarily occurs in mitochondria (Silva et al, 2008)⁴⁷. As detailed (Labbe et al, 2008⁴⁷; Fromenty et al, 1997)⁴⁸, valproate impairs mitochondrial function via several mechanisms, which can be briefly summarized as inhibiting mitochondrial FAO through the sequestration of coenzyme A (a cofactor mandatory for FAO), and also possibly by an electrophilic metabolite of valproate inactivating β -oxidation enzymes. In addition, valproate can induce MPT opening, which may explain why valproate-induced microvesicular steatosis is associated with liver cell death. These mechanisms of action of drugs, including valproate, on mitochondria are described in Figure 2 below.

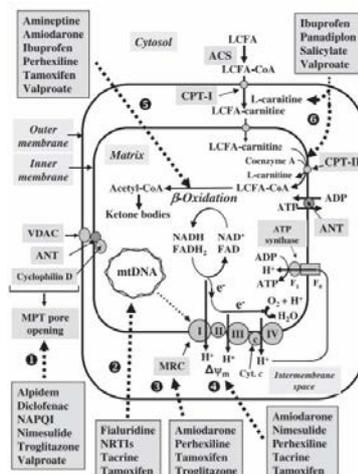
⁴⁵ Meyler's Side Effects of Drugs (16th edition; 2015)

⁴⁶ Labbe G, Pessayre D, Fromenty B. Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies. *Fundam Clin Pharmacol*. 2008 Aug;22(4):335-53.

⁴⁷ Silva MF, Aires CC, Luis PB, Ruiten JP, IJlst L, Duran M, et al. Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: a review. *J Inherit Metab Dis*. 2008 Apr;31(2):205-16.

⁴⁸ Fromenty B, Pessayre D. Impaired mitochondrial function in microvesicular steatosis. Effects of drugs, ethanol, hormones and cytokines. *J Hepatol*. 1997;26 Suppl 2:43-53.

Figure 1 - Main drug targets in the metabolism and energy production pathways in liver mitochondria (Labbe et al, 2008)⁴⁷



Valproic acid is transformed into valproyl-adenosine monophosphate (AMP), valproyl-acyl-coenzyme A (CoA), and valproyl-carnitine, and undergoes mitochondrial β -oxidation. Formation both CoA and carnitine valproate derivatives decreases free CoA and carnitine derivative levels in the liver. Because valproyl-CoA is presumably synthesized by medium-chain acyl-CoA synthetase in the mitochondrial matrix, the valproate-induced depletion of CoA affects the intra-mitochondrial pool of CoA. This explains why valproate impairs the β -oxidation of long-, medium-, and short-term chain fatty acids.

In addition to the sequestration of CoA and carnitine, a second, but hypothetical, mechanism of valproate inhibiting mitochondrial FAO might involve irreversible inactivation of mitochondrial enzymes by a metabolite formed through the successive actions of cytochrome P450 (CYP450) and mitochondria. This mechanism would explain why the toxicity of valproate is enhanced by the concomitant administration of enzyme-inducing AEDs (Fromenty et al, 1997)⁴⁹.

In 2014, Globa and colleagues (2014)⁴⁹ concluded that adverse effects of valproate in children with mitochondrial diseases were not dependent on CYP450 polymorphisms, but on mitochondrial metabolism of valproate.

Valproate interferes with intermediary metabolism in the mitochondria of both healthy patients and patients with latent inborn errors of metabolism (Lam et al, 1997)⁵⁰.

Valproate is generally regarded as the AED with the highest potential to induce mitochondrial toxicity (Finsterer et al, 2010;⁵¹ Nanau et al, 2013⁵²).

It has been demonstrated that underlying mitochondrial disorders are considerable risk factors for developing increased valproate toxicity, including the risk of hepatotoxicity, neuropsychiatric toxicity or lack of efficacy in certain forms of epilepsy. The product information was updated accordingly to include statements that reflect patients with underlying mitochondrial disorders being the most vulnerable to the action of valproate on mitochondria.

⁴⁹ Globa O, Gromyko O, Averianova N, Kuzenkova L, Pinelis V, Savost'yanov K. The individual tolerability of the valproic acid in children suffering from epilepsy with cytochrome p450 polymorphisms and mitochondrial disorders. *Epilepsia*. 2014;55(Suppl 2):143.

⁵⁰ Lam CW, Lau CH, Williams JC, Chan YW, Wong LJ. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. *Eur J Pediatr*. 1997 Jul;156(7):562-4.

⁵¹ Finsterer J, Segall L. Drugs interfering with mitochondrial disorders. *Drug Chem Toxicol*. 2010 Apr;33(2):138-51.

⁵² Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem*. 2013 Oct;46(15):1323-38.

Moreover, in 2017 Finsterer and colleagues⁵³ reiterated comments that AEDs with high mitochondrial toxic potential should be contraindicated in patients carrying POLG1 mutations. Finsterer and colleagues (2017)⁵⁴ postulated that in clinical practice mitochondrial epilepsy may be initially treated with AEDs with low mitochondrial toxic potential, AEDs with higher mitochondrial toxic potential only being considered in cases of treatment-refractory mitochondrial epilepsy.

Valproate-related liver toxicity involving various types of disorders including fatal fulminant hepatitis, has also been identified.

By hampering mitochondrial energy production and/or releasing mitochondrial pro-apoptotic proteins into the cytoplasm, such drugs can trigger the necrosis or apoptosis of hepatocytes, thus causing “cytolytic” hepatitis, which can progress towards liver failure. Milder mitochondrial dysfunction, sometimes combined with an inhibition of triglycerides, can induce microvacuolar steatosis. These lesions are benign in the short term, but can lead to steatohepatitis in the long term, which itself can progress to extensive liver fibrosis and cirrhosis (Labbe et al, 2008⁴⁷; Hargreaves et al, 2016⁵⁴).

Krähenbühl and colleagues (2000)⁵⁵ consider that mitochondrial disease represents a risk factor for valproate-induced fulminant hepatitis. They suggest that the typical histological findings of valproate-induced fulminant liver failure, namely microvesicular steatosis accompanied by necrosis of hepatocytes, indicate that inhibition of hepatic mitochondrial β -oxidation is a principal cause of valproate-induced liver failure. When valproate is activated to valproyl-CoA, the hepatic pool of free CoA is depleted, which represents a potential mechanism. Another mechanism may be direct inhibition of mitochondrial β -oxidation by metabolites of valproate, such as 2-N-propyl-4-pentenoic acid. Mitochondrial diseases are also a risk factor for valproate-induced fulminant hepatitis.

Wolters and colleagues (2017)⁵⁶ has suggested that valproate induces in human hepatocytes a crosstalk between nuclear DNA (nDNA) hypermethylation and mitochondrial DNA (mtDNA) hypomethylation, which plays a role in oxidative stress and steatosis development.

Valproate may also induce a Reye-like syndrome, characterized by hyperammonaemia, hypoglycaemia, microvesicular steatosis, and encephalopathy (Finsterer et al, 2010)⁵⁷. Reye-like syndrome results from opening of the MPT pore, leading to cytochrome-c release and caspase 3 activation.

Pancreatitis is a known reaction of valproate. Burkhart and colleagues (2010)⁵⁸ made a review about haemorrhagic pancreatitis. Valproate was found as associated with pancreatitis and the authors highlighted that the products associated with this reaction have mitochondrial toxicity; such findings could generate hypotheses about the mechanism for valproate induced-pancreatic toxicity.

In 2012, Wu and colleagues⁵⁹ conducted a study aimed at exploring the role of mitochondria in valproate-induced functional change in neutrophils. HDAC inhibitors, such as valproate, affect immune capacity via epigenetic regulation in cells and this study identified a novel mechanism whereby mitochondrial dysfunction in neutrophils were found to be responsible for a significant portion of

⁵³ Finsterer J, Scorza FA. Effects of antiepileptic drugs on mitochondrial functions, morphology, kinetics, biogenesis, and survival. *Epilepsy Res.* 2017 Oct;136:5-11.

⁵⁴ Hargreaves IP, Al Shahrani M, Wainwright L, Heales SJ. Drug-Induced Mitochondrial Toxicity. *Drug Saf.* 2016 Jul;39(7):661-74.

⁵⁵ Krähenbühl S, Brandner S, Kleinle S, Liechti S, Straumann D. Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. *Liver.* 2000 Jul;20(4):346-8.

⁵⁶ Wolters JEJ, van Breda SGJ, Caiment F, Claessen SM, de Kok TCM, Kleinjans JCS. Nuclear and Mitochondrial DNA Methylation Patterns Induced by Valproic Acid in Human Hepatocytes. *Chem Res Toxicol.* 2017 Oct 16;30(10):1847-54.

⁵⁷ Finsterer J, Segall L. Drugs interfering with mitochondrial disorders. *Drug Chem Toxicol.* 2010 Apr;33(2):138-51.

⁵⁸ Burkhart KK, Szarfman A, Lyndly J. Drugs associated with hemorrhagic pancreatitis in the food and drug administration adverse event database and mitochondrial toxicity. *Clin Toxicol.* 2010;48(3):295-6.

⁵⁹ Wu HM, Chang C, Huang W, Ho G. Valproic acid, a histone deacetylase inhibitor induces mitochondria-mediated immune deficiency in neutrophil. *Epilepsy Currents.* 2012;12(1)Suppl 1:1.271.

valproate-induced immune deficiency. This publication was the only one identified about this topic; the poster contains limited information and refers to *in vitro* study.

Since the years 2000, a growing body of evidence has indicated that peripheral markers of mitochondrial energy metabolism dysfunction, such as (a) elevated lactate, pyruvate, and alanine levels in blood, urine and/or cerebrospinal fluid, (b) serum carnitine deficiency, and/or (c) enhanced oxidative stress may be associated with neurodevelopmental disorders, particularly ASD. These biochemical abnormalities are accompanied by highly heterogeneous clinical presentations, which generally (but not always) encompass neurological and systemic symptoms that are relatively unusual in idiopathic autistic disorder. In some patients, these abnormalities have been successfully explained by the presence of specific mutations or rearrangements in their mitochondrial or nuclear DNA, and it is notable that valproate is not mentioned in any of these publications. Moreover, (Smith et al, 2012⁶⁰ ; Palmieri et al, 2010⁶¹), abnormal energy metabolism cannot be immediately linked to specific genetic or genomic mitochondrial defects or dysfunctions in patients with ASD.

No publications were identified describing the ability of valproate to interact with mitochondrial DNA that could have clinical consequences, such as impaired neurodevelopmental disorder or ASD.

In conclusion the literature overview described known toxic effects of valproate on mitochondria. Liver toxicity, Reye-like syndrome, pancreatitis and immune deficiency (leukopenia) are known side effects of valproate and mentioned in the product information.

In addition, in the literature a potential relationship between mitochondrial dysfunction and neurodevelopmental disorders, in particular autism was discussed. None of these publications mention valproate. Based on this information there is no clear evidence that mitochondrial dysfunction caused by valproate has been associated with the development of autism, and the currently available data do not warrant further investigation regarding the potential association between mitochondrial dysfunction and autism.

2.5. Clinical aspects

2.5.1. Data on efficacy

In previous review (2014)⁶², the efficacy of valproate was re-assessed and it was concluded that valproate is considered to be an effective drug in the treatment of epilepsy and of manic episodes 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, valproate should remain an option for female patients, but should be reserved for situations when other treatment alternatives have not been successful.

Treatment of generalised and focal epilepsy

For focal epilepsies, there are a number of alternatives to valproate with either superior or similar efficacy, therefore valproate should not be initiated as a first-line treatment. For the management of genetic generalised epilepsy (GGE), valproate can be the only therapeutic option for some patients for whom other treatments have failed, including pregnant women or WCBP.

Gesche and colleagues (2017)⁶³ suggests that about 20% of GGE patients who are drug resistant/have

⁶⁰ Smith M, Flodman PL, Gargus JJ, Simon MT, Verrell K, Haas R, et al. Mitochondrial and ion channel gene alterations in autism. *Biochim Biophys Acta*. 2012 Oct; 1817(10): 1796-802.

⁶¹ Palmieri L, Persico AM. Mitochondrial dysfunction in autism spectrum disorders: cause or effect? *Biochim Biophys Acta*. 2010 Jun-Jul; 1797(6-7): 1130-7.

⁶² [Assessment report](#) of 2014 review

⁶³ Gesche J, Khanevski M, Solberg C, Beier CP. Resistance to valproic acid as predictor of treatment resistance in genetic generalized epilepsies. *Epilepsia* 2017 Apr, 58(4): e64-e69.

refractory seizures became seizure free with valproate. Considering that GGE accounts for 15-20% of epilepsies and that 16-36% out of GGE patients are drug resistant, the proportion of patients with epilepsy who may only respond to valproate may be small but it clearly exists. The Joint Task Force with European academy of Neurology (Tomson et al, 2015)⁶⁴ also recommend that valproate may be offered as a first-line treatment for epilepsy syndromes where it is the most effective treatment, including idiopathic (genetic) generalized syndromes associated with tonic-clonic seizures. Further, they emphasize that situations exist (few alternatives and less effective treatments) where it is appropriate to prescribe valproate also to female patients of childbearing potential.

Alternative licenced monotherapy treatment options for primary generalised tonic-clonic seizures (GTCS), mainly in the context of GGE, are lamotrigine, phenobarbital, phenytoin, topiramate and valproate. These treatments may also be used in combination therapy. Based on current knowledge, valproate seems to have a higher teratogenic risk as compared to some other antiepileptic drugs, such as lamotrigine and levetiracetam. However, it is also known that not every patient respond to these alternative treatment options, and other therapies including valproate may be considered. However, phenobarbital and phenytoin may not be the best alternatives to valproate to treat GTCS, as use of these products can result in poor seizure control and increase the risk of injury or epilepsy-related death (Tomson et al, 2015)⁶⁶.

It is clear there is a subpopulation including WCBP and pregnant women who only respond to valproate, and discontinuation of therapy may be more harmful for the patient and the foetus. This has also been confirmed by the clinical experts consulted during this procedure.

Considering its risks, valproate should not be used as first line treatment. However seizure control during pregnancy is critical for the child's development and therefore, use of valproate in certain types of seizures during pregnancy maybe appropriate, despite the well-known risks. The risk of seizures due to discontinuation or switch of antiepileptic medications including valproate, seems to be higher during pregnancy and loss of seizure control in pregnancy is associated with severe consequences including maternal and foetal death. For this reason, in line with current recommendations in the product information, if a patient is planning to become pregnant, withdrawal of valproate or a switch to an alternative treatment should always be considered following a timely discussion with the physician to assess the benefits and risks for the patient. Treatment changes should be completed and adequately evaluated before conception. For valproate as well as for other treatments, the lowest effective dose should be established before conception.

Treatment of manic episodes in bipolar disorder

Valproate is effective in the management of acute mania for patients for whom lithium is contraindicated or not tolerated. Valproate is not indicated as maintenance treatment for episode-free only. Continuation of treatment after the manic episode can be considered in patients who have responded to valproate. As valproate is only indicated in patients for whom lithium is contraindicated or not tolerated, alternative treatments options are limited to atypical antipsychotics or electroconvulsive therapy (ECT).

The existence of group of patients who may only respond to valproate for the treatment of bipolar disorder is not established based on the current data. One MAH (Sanofi) highlighted that even for severely ill patients, whose mania is treatment-resistant, ECT appears a possible treatment, including during pregnancy. According to the product information, the antipsychotics aripiprazole, quetiapine,

⁶⁴ Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, Kälviäinen R, Trinka E. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia*. 2015 Jul; 56(7):1006-19.

risperidone and olanzapine have shown some extent of reproductive toxicity in animal studies. However, due to limited information, the risk in humans is unknown.

Olanzapine, however, has been associated with hyperglycaemia and new-onset diabetes in the mother, which, if poorly controlled, can cause developmental toxicity. Olanzapine should only be used when clearly necessary and if the potential benefit justifies the potential risk to the foetus.

All antipsychotics may cause adverse drug reactions to new-born infants when exposed during the third trimester, including extrapyramidal and/or withdrawal symptoms.

Electroconvulsive therapy (ECT) and direct-current cardioversion do not seem to pose a significant risk to the foetus. Following a recently published systematic literature review regarding the ECT in pregnancy (Leiknes et al, 2015)⁶⁵, the most frequent adverse effect of ECT in the mother was premature contractions and labour (28%), whereas in the foetus it was bradyarrhythmias (43%).

The current product information provides the same precautions and warnings for epilepsy and bipolar disorder, i.e. other therapies should be considered first, WCBP should use contraceptive measures and use of valproate during pregnancy avoided. However, based on the current available data, the necessity to differentiate between the two indications was identified because the medical need for treatment in bipolar in WCBP and pregnant women might be different from the need in epilepsy. Results of a study (CNAMTS study - part I)⁶⁶ conducted in France showed that pregnancies exposed to valproate occur, and that the majority of pregnant women receiving valproate for the treatment of bipolar disorders, switch or discontinue this therapy early during pregnancy (mostly in the first trimester), suggesting that valproate treatment during pregnancy may not always be necessary. Although limited, data from post-marketing spontaneous reports suggest discontinuation of valproate in early pregnancy.

Prophylaxis of migraine

In some EU Member States valproate is authorised for the prevention of migraine attacks. There are only limited data on the efficacy of valproate in the management of migraine prophylaxis in WCBP. In view of the risks of valproate use during pregnancy, and the available therapeutic alternatives for the treatment of acute migraine attacks, with the outcome of the 2014 referral, the use of valproate in the treatment of migraine was more restricted, (as compared to epilepsy and bipolar disorders indications), and contraindicated in the prophylaxis of migraine attacks in pregnancy and WCBP who do not use effective methods of contraception during treatment with valproate. Pregnancy must be excluded before starting valproate treatment.

No new data on efficacy has become available regarding the need for valproate for migraine attacks in WCBP or pregnant women as compared to the previous referral.

2.5.2. Data on safety

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 medicines. More recently data have also shown an association between *in utero* exposure to valproate and the risk of developmental disorders.

⁶⁵ Leiknes K.A., Cooke M. J., Jarosch-von Schweder L., Harboe I and B. Høie, (2015); Electroconvulsive therapy during pregnancy: a systematic review of case studies, Arch Womens Ment Health, 18: 1–39.

⁶⁶ [http://ansm.sante.fr/Dossiers/Valproate-et-derives/Valproate-et-derives/\(offset\)/0](http://ansm.sante.fr/Dossiers/Valproate-et-derives/Valproate-et-derives/(offset)/0) or <http://www.igas.gouv.fr/IMG/pdf/2015-094R.pdf>

As already known, teratogenic risks are associated with the use of valproate in pregnant women. Data derived from a meta-analysis (including registries and cohort studies) (Meador et al, 2008)⁶⁷ 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, where 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 (AEDs) (Weston et al, 2016)⁶⁸.

Available data showed an increased incidence of both 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.

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).

Since the previous valproate review more research was done. One of the MAHs (Sanofi) performed a literature review which identified four recent reviews: Weston et al, 2016⁶⁸; Bromley et al, 2014⁵; Vanya et al, 2015⁶⁹; and Thomas et al, 2016. The findings in these reviews as well as evaluation of information from cases of VPA exposed pregnancies spontaneous reporting systems are consistent with the known magnitude and severity of risks associated with *in utero* exposure to valproate.

The French national authority submitted a report (CNAMTS study - part II)⁶⁶ that studied the teratogenic risk of valproate in pregnant women in France. Overall the results concerning the congenital malformations identified in the study are in line with what is expected for VPA and with the outcome of the extensive EU review of all available data which concluded in 2014. It is acknowledged that the teratogenic risk of VPA seems less pronounced in bipolar patients compared to exposed epilepsy patients but it is too early to draw any robust conclusions. There are limitations of this study which include that several factors such as dosing, information on drug exposure and the disease itself on the observed teratogenic risks could not optimally be studied.

⁶⁷ Meador K, Reynolds MW, Crean S 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

⁶⁸ Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev.* 2016 Nov 7;11:CD010224.

⁶⁹ Vanya, M., Arva-Nagy, N., Szili, K., Szok, D., and G., Bartfa (2015); Effects of maternal epilepsy and antiepileptic therapy in women during pregnancy. *Ideggyogy Sz* 68(3-4): 105-112

It is also noted that whilst valproate seems to have a higher teratogenic risk than alternatives, the latter are not exempt of such risk. In a recent publication (Veroniki et al, 2017)⁷⁰ the authors concluded that for major congenital malformation (MCMs), ethosuximide (OR, 3.04; 95% CrI, 1.23–7.07), valproate (OR, 2.93; 95% CrI, 2.36–3.69), topiramate (OR, 1.90; 95% CrI, 1.17–2.97), phenobarbital (OR, 1.83; 95% CrI, 1.35–2.47), phenytoin (OR, 1.67; 95% CrI, 1.30–2.17), carbamazepine (OR, 1.37; 95% CrI, 1.10–1.71), were significantly more harmful than control but lamotrigine (OR, 0.96; 95% CrI, 0.72–1.25) and levetiracetam (OR, 0.72; 95% CrI, 0.43–1.16) were not. Lamotrigine and levetiracetam were also shown to have the lowest teratogenic risks in a Cochrane review, while valproate was shown to have the highest risks in women with epilepsy when compared to women without epilepsy and women with untreated epilepsy (Weston et al, 2016)⁶⁸.

2.5.2.1. Current risk minimisation measures

Following the previous referral in 2014 several risk minimisation measures have been implemented to minimise and inform HCP and patients about the risks related to the exposure to VPA during pregnancy: changes to the product information (restriction of use in WCBP in the prophylaxis of migraine, recommendation to be used only with effective contraception in epilepsy and bipolar disorders), a HCP guide, a patient booklet, an acknowledgement risk form.

In addition, a direct healthcare professional communication (DHPC) was circulated.

2.5.2.2. Effectiveness of current risk minimisation measures

Data on the effectiveness of currently implemented risk minimisation measures became available from various sources including the PASSs (joint DUS and joint HCP Survey) imposed as a condition to the MA following the previous referral. Further, a number of national initiatives have been undertaken in MSs as well as input from professional and patient representative organisations, which also provided information useful in the evaluation of the effectiveness of the current risk minimisation measures. It is important to note that the period after implementation of the risk minimisation measures agreed in the referral and afterwards (2015-2016) is rather short. However the data from different sources confirmed the need for improved risk communication.

This is briefly summarised below, including evaluation of results from DUSs with focus in change of patterns of valproate prescriptions in WCBP and pregnant women over time (stratified *per* country and indication).

Data regarding exposure to valproate in women of childbearing potential (WCBP)

Detailed data on the prescription of valproate in WCBP and pregnant women after the 2014 referral was submitted:

I. Intercontinental Marketing Services (IMS) data

The MAHs submitted International Marketing Services (IMS) data that reflects all prescriptions between 2011 and 2016 in France, Spain, Germany, Italy and UK. Based on the IMS data analyses, the prescription rates of valproate in WCBP for all indications together decreased at similar rates in the UK, France, Germany and Italy (by 27%, 25%, 26% and 20%, respectively) while only a slight decrease of 1.5% was observed in Spain.

⁷⁰ Veroniki et al. 2017; Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes, BMC Medicine 15:95

More specifically in epilepsy, the valproate prescriptions within the 2-year post implementation period of the additional risk minimisation measures (RMM) compared to the 2-year pre-RMM implementation period decreased in all 5 countries. By decreasing order of prescription frequency, the prescriptions decreased by 49% in France, 40% in Spain, 38% in Germany, 17% in Italy and 16% in the UK.

The IMS data show that in all countries except France, valproate was more often used in WCBP for epilepsy indication than for bipolar disorders (BP) indication. Data from CPRD (Clinical Practice Research Datalink - UK general practitioners' data) and French CNAMTS study show similar trend as observed from IMS data (discussed below in this report). Although in France the absolute number of valproate prescriptions in WCBP seems higher for BP as compared to epilepsy, the proportion of French WCBP with BP treated with valproate is comparable to those estimated in Germany and the Netherlands/Nivel data (20-25% after implementation of the additional RMMs). A possible explanation for the high absolute number of valproate prescriptions for WCBP with BP might be a larger population of WCBP with BP in France as compared to other EU countries. It could have also been influenced by other contributing factors such as differences in diagnostic criteria and/or coding for BP leading to misclassification of diagnosis.

II. Interim report of the joint DUS

The DUS data reflect only selected HCPs data from involved countries. The data from the joint DUS are limited, as the study is ongoing and the small sample size for indication-specific data in the post-referral period should be considered when interpreting the results. However, the preliminary conclusions are that the number of WCBP using valproate (both initiation and repeat prescriptions), regardless of indication, has decreased in Sweden (only 5 months data) Germany, France, Spain and United Kingdom after implementation of the RMM. However, the preliminary data suggest that there is no evidence of improved prescribing behaviour after implementation of the RMM, as the proportion of WCBP in whom the prescribers considered other drugs before initiating treatment with valproate did not increase in the post-implementation period. At present the PRAC has assessed the second interim report of this DUS study and details as well as the results-to-date are presented below:

Study design

Multinational cohort study based on existing data sources using a pre- and post-design to examine the changes in the prescribing patterns of valproate.

The study was conducted in the outpatient setting in five European countries (France, Germany, Spain, Sweden and the United Kingdom).

The overall study period was divided into two periods with respect to the implementation of risk minimisation measures as follows:

- A 3-year pre-implementation period
- A 3-year post-implementation period

Pre-implementation period (3-year duration)

The pre-implementation period covers a three-year period before finalisation of the 2014 referral and the distribution of the DHPC. The DHPC has been distributed in December 2014, in the selected countries and in January 2015 in the UK at the end of the previous EU review.

This pre-implementation period was considered as a baseline period and was divided into two sub-periods regarding the possible effect of the PRAC referral announcement in October 2013 on the prescribing practices. The two sub-periods were defined as:

- *Main period (~21 months' duration):* Starting 3 years before the date of DHPC distribution and ending at the date of PRAC referral announcement
- *Transition period (~15 months' duration):* Starting at the date of PRAC referral announcement and ending at the date of DHPC distribution

The period between the pre- and post- implementation periods is country-specific because the dates of DHPC and educational materials' distribution vary by country. This period was not considered for the analysis.

Post-implementation period (3-year duration)

The post-implementation period starts after the first day of distribution of approved educational materials by national competent authorities in the selected countries up to 3-years after the distribution. This period is divided into two sub-periods regarding a possible delayed full effectiveness of the educational materials during the first 6 months after the distribution. The two sub-periods were defined as:

- *Transition period (6 months duration):* The first 6 months after the date of the educational materials' distribution in each country.
- *Main period (6 months to 30 months, for the consecutive study reports):* Starting 6 months after the date of the educational materials' distribution and lasting for an additional 30 months (until 36 months after the date of the educational materials' distribution).

The study periods are defined per country based on the exact date that the DHPC or educational material was distributed.

Results for the entire 36-month pre-implementation period and 18-month post-implementation period (11 months in Sweden); the two main study periods were a 21-month pre-implementation period and a 12-month post-implementation period (5 months in Sweden).

The study population included all patients receiving valproate prescriptions in the outpatient setting during the pre-defined periods (pre- and post- implementation periods) in the selected databases of the five target countries. Patients were included in the respective study cohorts, for female patients who had at least one prescription of valproate in oral formulation. No exclusion criteria were applied.

Four longitudinal patient-level electronic medical records databases⁷¹ were used for the second interim report.

The national coverage of these data sources with respect to physician universe ranges from about 3% in France, Germany and Spain to about 8% in UK. The national coverage of registry data in Sweden is due to the nature of national registries nearly 100%.

Outcome parameters

The primary outcome parameter was defined as proportion of valproate prescriptions with at least one medication used prior the valproate initiation and related to the valproate indication (epilepsy, bipolar disorder, migraine headaches) within 12 months before the valproate initiation date. The analysis was based on incident prescriptions. The results were presented as percentages of prescriptions with previous medication related to valproate indication in pre- and post-implementation periods.

The primary objective of this study was to assess the effectiveness of the RMMs in the outpatient setting by comparing the prevalence of prior medication use related to the indication of valproate

⁷¹ IMS® Disease Analyzer for France and Germany, IMS® LPD for Spain, CPRD for UK, National Health Registries of Sweden

initiation in females before and after implementation of RMMs. An increase of this parameter in the post-implementation period compared to the pre-implementation period was considered as a success criterion of RMMs implementation.

The secondary outcome parameters studied were diagnoses of interest in medical history, use of hormonal contraceptives or Intrauterine device (IUD) in medical history, valproate indication, valproate treatment characteristics (prescribed daily dose and prescription duration, concomitant medications related to valproate indication, concomitant use of hormonal contraceptives or IUD. Proportion of pregnancies exposed to valproate (at least one valproate prescription during pregnancy within the defined study period) was calculated in relation to the overall number of pregnancies in patients included in the study within the defined study periods.

In case information on pregnancy trimester or start date or delivery/end of pregnancy date was not available in the data source, a pregnancy was considered as exposed to valproate if at least one valproate prescription was issued within 90 days before the first pregnancy record or within 180 days after the first pregnancy record. If the information on trimester or start date or delivery/end of pregnancy date was available, the pregnancy was considered exposed if at least one valproate prescription was recorded in the period between assumed dates of pregnancy start and delivery/end of pregnancy.

Valproate indication (diagnosis related to the valproate prescription) was evaluated as a categorical variable on prescription level.

Demographic characteristics

Overall, the mean age in patients receiving valproate ranged from 45.3 years to 57.8 years in the target countries, whereas the highest mean age was found in Germany.

Proportion of patients aged 13 to 49 years varied in main pre-implementation period between 34.5% in Germany and 61.0% in Spain. In the main post-implementation period this proportion decreased numerically in all countries and ranged from 32.6% in Germany to 50.3% in the in Spain. The strongest decrease rates were found in France and in patients managed by neurologists/psychiatrists in Spain (ca. 11%). The proportion of patients in the age group ≥ 50 years increased in the post-implementation period in all countries.

Diagnosis

Epilepsy was the main indication for valproate in all prescriptions in Germany, in Spain, in Sweden and in UK continuously over both study periods.

In the age group 13 to 49 years the proportion of prescriptions with indication epilepsy was about 3% to 11% higher compared to the proportion in all prescriptions (Germany, Spain, UK). In Sweden proportions were similar in the overall group and in the age group 13 to 49 years.

In France, also the main indication for valproate prescriptions was epilepsy, with 20.7% and 26.0% in the age group 13 to 49 years to a lower extent than in the other countries in both study periods.

Bipolar disorder was recorded in less than 20% of all valproate prescription in France, Germany, and UK, whereas in Spain this diagnosis was more frequent with around 30% and slightly lower in the age group 13 to 49 years. In Sweden, bipolar disorder was the indication for 37.9% to 40.2% of all prescriptions (39.5% in the age group 13 to 49 years).

Migraine headaches were the indication in a very limited number of valproate prescriptions (<1% of all prescriptions in France, Germany and Sweden to 8% in neurologists/psychiatrists panel in Spain).

Other diagnoses than epilepsy, bipolar disorder and migraine headaches were found in 17% to 28% of all valproate prescription in Germany and Spain. In France, the proportion of other diagnoses is around 50% of all valproate prescriptions. Diagnoses related to schizophrenia, anxiety disorder, unspecified nonorganic psychosis, organic personality disorder, but also unspecified dementia, unspecified mental retardation or Alzheimer disease. This study mirrors real-life use of valproate and therefore, off-label needs to be considered. Valproate use for the treatment of schizophrenia for example is described in the scientific literature (Horowitz et al, 2014)⁷². In Sweden and UK, other diagnoses for valproate are not available.

Indication for valproate was unknown in 14% to 15% of all prescriptions in France, in 5% to 8% in Germany, less than 2% in Spain, 13% to 15% in Sweden and around 20% in UK. Comparable figures are observed for valproate prescriptions for women aged 13-49.

Daily dose and prescription duration

The mean prescribed daily dose in all prescriptions varied between 786 mg and 1,025 mg in the pre- and between 862 mg and 1,019 mg in the main post-implementation periods. The mean prescribed daily dose was slightly higher in the age group 13 to 49 years and ranged from 831 mg to 1,078 mg in the main pre- and from 892 mg to 1,100 mg in the main post-implementation period.

The mean prescription duration in all prescriptions varied between 28 days and 56 days in the pre- and between 28 days and 59 days in the main post-implementation period. The results were similar in the age group 13 to 49 years. The estimated mean prescription duration ranged from 31 days to 59 days in the main pre- and from 29 days to 61 days in the main post- implementation period.

No major differences in prescription duration or daily dose between the pre- and post-implementation period are observed for any country.

Concomitant medication

Overall, the proportion of incident valproate prescriptions with concomitant use of relevant medications related to the valproate indication ranged from 51.5% to 81.9% in the main pre-implementation period. In the post-implementation period the proportion was similar in France, Germany and Sweden. While in Spain it was recorded in a lower proportion of valproate prescriptions than in the pre-implementation period, and in UK a higher proportion was found.

In the age group 13 to 49 years the proportion of relevant concomitant medication ranged from 44.4% in Germany to 75.3% in Spain in the main pre-implementation period. In the post-implementation period the proportion was similar in most of the countries with small differences.

No clear pattern could be identified between the two periods and between countries.

Concomitant use of hormonal contraceptives or IUD in the age group 13 to 49 years

Proportion of valproate prescriptions with records on concomitant use of hormonal contraceptives or IUD in the age group 13 to 49 years was around 10% in France, ranged from 34% to 40% in Sweden and varied between 2% and 6% in Spain and UK in main study periods in all prescriptions and in incident prescriptions. In Germany, no records on concomitant use of hormonal contraceptives or IUD were available in the data provided.

No clear changes in the proportion of concomitant use of IUD or hormonal contraceptives during valproate prescriptions of females aged 13-49 between the two periods were observed in any of the countries.

⁷² Horowitz E, Bergman LC, Ashkenazy C, Moscona-Hurvitz, Grinvald-Fogel H, Magnezi R. Off-label use of sodium valproate for schizophrenia. PLoS One. 2014 Mar 24; 9(3):e92573.

Pregnancy

Proportion of pregnancies exposed to valproate (at least one valproate prescription during pregnancy within the defined study period) was calculated in relation to the overall number of pregnancies in patients included in the study within the defined study periods.

Overall, 1,244 pregnancies including 435 exposed to valproate (35.0%) from the entire 36-month pre-implementation period and 264 including 76 exposed to valproate (28.8%) from the entire post-implementation period were available.

The majority of pregnancies (n=730) were identified in the entire 36-month pre-implementation period in Sweden, 205 were exposed to valproate. In the entire 11-month post-implementation period 141 pregnancies were documented in Sweden, 34 of them were exposed to valproate. The proportion of pregnancies exposed to valproate related to the overall number of pregnancies in valproate users in Sweden was 30.5% in the main pre-implementation period and 24.0% in the main post-implementation period, indicating a decrease of exposed pregnancies.

In UK, 428 pregnancies were identified in the entire 36-month pre-implementation period, 172 of them were exposed to valproate; in the entire 18-month post-implementation period 105 pregnancies were documented, 28 of them were exposed to valproate. The proportion of pregnancies exposed to valproate related to the overall number of pregnancies in valproate user decreased from 40.9% in the main pre-implementation period to 24.2% in the main post-implementation period.

In France, 34 pregnancies were identified in the entire 36-month pre-implementation period, 20 of them were exposed to valproate; two pregnancies, both exposed to valproate, were recorded in the entire 18-month post-implementation period.

In Spain, the corresponding figures were 51 pregnancies in the entire 36-month pre-implementation period including 37 exposed pregnancies; 16 pregnancies were documented in the entire 18-month post-implementation period including 12 exposed pregnancies.

Only one pregnancy exposed to valproate in the entire pre-implementation period was identified in Germany.

The currently ongoing joint (DUS) collects real-world healthcare information from various EU healthcare databases and aims to detect physician prescribing behavior in response to the RMMs. Data related to prescribed oral hormonal contraception and intra-uterine devices are captured in databases used as data sources for the current DUS, however other methods of contraception are not, which would be a limitation of data derived from this source. Also, data related to pregnancies are not comprehensively captured in all of the databases used in the current DUS.

III. Joint HCP (prescribers) survey

A joint cross-sectional, multinational and non-interventional PASS Healthcare Professionals (HCP) survey among psychiatrists, neurologists, general practitioners (GPs) in 5 EU Member States (Germany, Sweden, Spain, France and UK) (2016) via web questionnaires was designed to assess the effectiveness of the DHPC and educational materials, implemented as part of RMM, by ascertaining the proportion of targeted physicians who understood and implemented the latest prescribing conditions and safety information about valproate provided in the DHPC and educational material.

Specific objectives were to evaluate the proportion of prescribers who only prescribe valproate for epilepsy and bipolar disorder in women if other treatments are ineffective or not tolerated; the proportion of physicians who ensure that the treatment of epilepsy or bipolar disorder is supervised by

a doctor experienced in treating these conditions; the proportion of physicians who consider alternative treatments if a female patient becomes or plans to become pregnant during valproate treatment; regularly review the need for treatment and reassess the balance of the benefits and risks for female patients taking valproate and for girls reaching puberty; the proportion of physicians who inform patients of the risks of taking valproate during pregnancy; the proportion of physicians who advise female patients taking valproate medicines about effective contraception during their treatment.

The survey has been completed by a total of 1153 physicians of which 255 were from France, 254 were from Germany, 244 were from Spain, 136 were from Sweden and 264 were from the United Kingdom.

The HCP survey indicated that 40% of the participating HCPs mentioned that they did not recall receipt of either the DHPC or the educational materials. While in some cases this might be due to a recall bias, the MAHs confirmed that the educational materials were not sent to all relevant HCPs, e.g. in the UK the educational materials have not been sent to 40% of the HCPs.

Overall, about 35% of the HCPs in all surveyed countries did not consider that valproate should not be prescribed in WCBP unless other treatments are ineffective or not well tolerated.

Further, only 49% of HCPs noted that they re-evaluate the benefit risk balance of treatment with valproate when the child reaches puberty and 54% of the HCPs would evaluate the benefits against risks during each routine treatment review.

GPs and other specialists may be less aware of valproate prescribing conditions compared to neurologists and psychiatrists, while most of the valproate prescriptions are made by GPs (at least in the countries participating in the survey). The receipt of the educational materials was also lower in GPs compared to specialists.

The survey data also indicated that those who could recall the receipt of the educational materials and/or DHPC had a better knowledge on the prescribing conditions of valproate.

IV. Data from Registries on pregnancies with antiepileptic treatments

Currently there are several ongoing initiatives for registries for anti-epileptic drugs (AED) when used during pregnancy such as, EURAP (an international Registry of Antiepileptic Drugs and Pregnancy), European network of Teratology information service (ENTIS) in different MSs and UK Epilepsy and pregnancy registry.

The ENTIS and EURAP registries both have follow-up services for exposed pregnancies. The information collected during follow-up by ENTIS includes details on prenatal diagnostics, course and complications of pregnancy and delivery, gestational age at delivery, birth weight, head circumference, congenital anomalies, and postnatal disorders are obtained. The follow-up of the new-born should cover paediatric check-ups at least until the age of one month.

The EURAP collects follow-up information at three different time points: at 2, 6 and 12 months after the birth (Tomson et al, 2011⁷³; Tomson et al, 2015⁷⁴). During the follow-up (at 2 months after the

⁷³ Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E, Vajda F; EURAP study group.. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol.* 2011 Jul;10(7):609-17.

⁷⁴ Dose-dependent teratogenicity of valproate in mono- and polytherapy An observational study Torbjörn Tomson, Dina Battino, Erminio Bonizzoni, John Craig, Dick Lindhout, Emilio Perucca, Anne Sabers, Sanjeev V. Thomas, Frank Vajda and For the EURAP Study Group

birth), information collected includes exposure to risk factors during the third trimester of pregnancy, detailed history of exposure to drugs during the third trimester of pregnancy and current pathological conditions. For women having epilepsy, details on type and frequency of seizures during the third trimester of pregnancy and seizures at delivery are obtained. Further the EURAP collects data on the date and site of delivery, obstetric complications and mode of delivery, clinical status of child, detailed description of any congenital abnormality and the post-mortem examination of child (if applicable). In the subsequent follow-up (i.e. at 6 and 12 months after the birth), additional information regarding the health outcomes in children is collected including birth defects. Identification of developmental disorders may be more challenging using these registries.

Considering that the EURAP and ENTIS registries have follow up services, they might provide useful support for further follow-up in women using VPA and identification of children with valproate foetal syndrome.

The UK Epilepsy and pregnancy registry was started in 1996, initially as a research project to monitor the effects of anti-epileptic drugs in the UK to detect congenital abnormalities and developmental delay. The register has now well over 10,000 recorded pregnancies in epilepsy and has reported abnormalities such as spina bifida, cleft palate and heart defects in association with valproate as well as neurodevelopmental delay, learning difficulties and autism.

The information that can be derived from the registries mentioned above, as well as from national and international registries (see table 3 below), may provide epidemiological data on the foetal anticonvulsant syndrome (FACS). The PRAC is requesting the MAHs to conduct a study using the existing registries on antiepileptics to further characterise the FACS in children with valproate *in utero* exposure as compared to other anti-epileptic drugs.

Table 3. List of Registries on exposure of pregnancies to anti-epileptic treatments

Name (publication)	Location	Number of patients enrolled and period	Registry owner	Outcomes	Advantages / Limitations
EURAP – Central Registry of Antiepileptic Drugs and Pregnancy (Interim Report - May 2017)	42+ countries	22 700+ pregnant women with epilepsy, including 1 800+ exposed to VPA, since 1999	Consortium of independent research groups. Chairman: Dr. Tomson (Karolinska University Hospital)	MCMs	Ongoing, records of pregnancy before 16 weeks and of pregnancy outcomes (completed or not)/ Follow-up of children up to 3 months
EURAP – NCEP (extension protocol) (Eriksson, Gaily, 2012)	EURAP centres in Belgium, Netherlands, Denmark, Finland, Germany, Italy, Norway, Sweden	Enrollment time window 2009 – 2013, target of at least 95 children in each monotherapy group	Protocol authors from University of Tampere and Helsinki University Hospital in Finland	NDD	Follow-up of children up to 7 years, adjustment for known risk factors for NDD / Status unknown, no publications
National registries from Nordic European countries (Christensen 2013)	Norway, Sweden, Denmark and Finland	Continuous (e.g., in Denmark 508 children exposed to VPA <i>in utero</i> born between 1996–2006)	National	Any condition with ICD code (MCM, ASD)	Ongoing, systematic collection of medication exposure; control group (general population) / Pregnancies leading to abortion not included, no records of NDD, smaller sample size
National prescription database linked with hospital data	France	Continuous, linkage mother–child since 2011	National, access to research/institute teams only	Any condition with ICD code diagnosed at hospital	Ongoing, systematic collection of medication exposure; control group (general population) / No records of NDD
North American-AED Pregnancy Register (Hernandez-Diaz et al. Neurology 2012)	USA and Canada	About 9 300 pregnant women with epilepsy, including about 330 exposed to VPA since 1997	Massachusetts General Hospital in Boston	MCMs	Ongoing, records of pregnancy outcomes (completed or not); external comparison group/ Follow-up of children up to 5 days

V. Data from the national competent authorities in the Member States

The data from different sources at the national level in the member states (MS) were collected, indicating that there was a difference in the prescribing trend of valproate when comparing indication-specific data.

France

a. CNAMTS⁷⁵ study (Part I and Part II) (August 2016)

As per a request of French authorities, a retrospective cohort study was conducted by one MAH (Sanofi) in the national Social Security database (SNIIRAM) to assess frequency of exposure to valproate during pregnancy from 2007 to 2014 and of use in WCBP from 2007 to beginning of 2016.

The study population consists of women who became pregnant in France between the 1 January 2007 and 31 December 2014, the pregnancy ending in birth or any other outcome (ectopic pregnancy, miscarriage, voluntary abortion, medical termination, etc.). Part I of this study dealt with the utilisation of antiepileptic products including valproate products and part II with the teratogenic outcomes. This study is referred in several sections of this report and each time the results of the relevant part are cited.

The results of this study (Part I) highlighted the continuing high level of exposure to valproic acid among pregnant women and WCBP in France. Thus, 1,333 pregnancies in 2014 were exposed to valproic acid, and 51,512 women of reproductive age were exposed to valproic acid in the first quarter of 2016. These levels remain a concern despite a significant decrease in the frequency of exposure among pregnant women by 42.4% (from 2,316 in 2007 to 1,333 in 2014) and women of childbearing age, decreased by 32% (from 122,382 in 2007 to 83,712 by 2015), whose decrease is likely due to a change of prescription to other therapeutic options (including lamotrigine) and which seems to have increased in 2015 and early 2016. Moreover, the results show contrasting situations in the context of pathological prescribing of valproic acid and the socio-demographic characteristics of women.

b. Pharmacist survey in France

Following a request of the French authorities, an observational, prospective, survey to evaluate the implementation of new conditions for the prescription and dispensing of valproate at the level of by pharmacists, was conducted in France in 2017.

Its primary objective was to verify the implementation of new conditions for the prescription and dispensing, applicable to oral forms of valproate and related substances, for use in female adult outpatients, at pharmacists level.

As secondary objective, the rate of compliance with prescription conditions, according to the proprietary medicine of the prescriber, the product prescribed, the region of the pharmacy and the age range of patients were measured. Another secondary objective was the description of the dispensing conditions: the proportion of pharmacists who dispense the product even though it has been inappropriately prescribed, and details of the dispensation in the event of inappropriate prescription.

⁷⁵ [http://ansm.sante.fr/Dossiers/Valproate-et-derives/Valproate-et-derives/\(offset\)/0](http://ansm.sante.fr/Dossiers/Valproate-et-derives/Valproate-et-derives/(offset)/0) or <http://www.iqas.gouv.fr/IMG/pdf/2015-094R.pdf>

The aim was to collect information from 1,000 patients between the age 2-49 years old (in two groups 100 patients between 2-12 years old and 900 patients between 13-49 years old) across the French territory.

This four month survey revealed that the new prescription and dispensing conditions for valproate in women, female adolescents and women of childbearing age are observed by healthcare professionals in a third of cases, while treatment risk information forms were presented in 33% of cases and prescriptions were issued by a specialist within the previous year in 75% of cases.

Prescription conditions were found to be more frequently observed in the case of prescriptions for an initial course of treatment. In such instances, treatment risk information forms were signed in 46% of cases and prescriptions were issued by a specialist in 91% of cases.

Due to missing forms, the rate of compliance under prescription conditions ranges from 50% for prescriptions issued by neurologists to 13% for those issued by paediatricians.

In the majority of cases where the prescription conditions were not observed, pharmacists did actually dispense the treatment, dispensing on average just one bottle. Furthermore, before dispensing the treatment, 89% of pharmacists ensured that the patients understood the risks of becoming pregnant, while 86% reminded them of their obligation to attend an appointment with an authorised specialist each year.

United Kingdom

a. Clinical Practice Research Datalink (CPRD) study)

A retrospective analysis was conducted in CPRD to look at prevalent and new use of valproate in women from January 2010 to June 2016.

Rate of use of valproate in WCBP decreased from 30.4 per 10 000 women in Jan-Jun 2010 to 22.7 per 10 000. Despite observed fluctuations, rate of new use of valproate in WCBP also decreased from 2.18 per 10 000 women to 1.26 per 10 000 women.

b. UK Patient survey

As requested by the MHRA, a patient survey was conducted from April to June 2016 in three UK Epilepsy charities in women with epilepsy aged 18 to 50 years old. A total of 2,788 answered and 624 were currently taking valproate.

Of these women, 80% were aware of the risk associated with *in utero* exposure to valproate, 20% received any of pharmacy card, patient booklet, checklist or verbal advice.

Despite a low rate of distribution of information or educational materials dedicated to patients in the months right after the implementation of patient card in the UK, majority of patients are aware of the risks and may have received the information from other sources.

The Netherlands

The Dutch data (Nivel, Netherlands institute for health services research; 2011-2015) showed a decrease in the proportion of patients that were prescribed valproate among all patients with diagnosis of epilepsy, as well as in pregnant women and in WCBP. For bipolar disorder, no decreasing trend was observed and the proportion has been stable over the years. However, in view of the limited total number of WCBP treated for bipolar disorders, these results should be interpreted with caution.

A downward trend in valproate use during pregnancy was observed in a cohort of pregnant women already in the period before the referral started, i.e. between 2003 and 2012. At the same time an upward trend in levetiracetam and lamotrigine use was also observed (Van Puijenbroek 2014)⁷⁶.

Other Member states

Responses of MSs to a EMA request for information included available crude data from Germany and Ireland (Murphy et al, 2016)⁷⁷, that pointed towards a decreasing trend of valproate prescription in WCBP after the 2014 referral while the available data from Denmark, Spain and Lithuania did not indicate changes in valproate prescribing.

VI. Exposed pregnancies

The interim results of the joint DUS study suggest a decrease in the number of pregnancies after implementation of the RMM however no firm conclusions can be made based on the DUS data due to numbers collected to-date. The French study (CNAMTS study part I) shows that the majority of the exposed pregnancies concerned BP patients (57%). This study showed a decreasing trend between 2007-2014 in prescription of VPA for in pregnant women, which was stronger for epilepsy (-56%) compared to bipolar disorder (-18%). Data from Nivel (the Netherlands) suggest very low numbers of pregnancies exposed to VPA.

The data from post-marketing spontaneous sources indicate that there were 484 cases reported in relation to pregnancy exposure in European countries in 2015-2016. The majority of these pregnancy exposure cases (64%) have been reported in France. The pregnancy reporting rates for epilepsy indication have been increasing in France in 2015-2016 as compared to the previous years (more than 15-fold increase in the reporting rate), while in other countries the pregnancy reporting rate decreased (UK, Germany, Italy) or remained low (Spain).

Conclusions regarding drug utilisation data

In general, the available data show decreasing trend in prescription of valproate in WCBP for epilepsy. The decreasing trend was less pronounced for the BP indication: a decrease of valproate use was observed in France, Italy, Sweden and UK, which in France was less compared to epilepsy. In the Netherlands and Germany prescription for BP remained more or less stable (and relatively low) over time; in Spain an increase in absolute number of valproate prescription for BP in WCBP has been observed in the post-implementation period. It should be taken into account that some studies had only a limited period of post-referral data which might have precluded the observation of ongoing changes in valproate use.

A decreasing trend in valproate use was observed already before implementation of the RMM agreed in the 2014 referral. For example, this is seen in the UK data. The French CNAMTS study also showed a decreasing trend of valproate use in WCBP for both epilepsy and BP indication, which decreased further after the referral in 2014. In Ireland a decreasing trend in use of valproate in WCBP for epilepsy was

⁷⁶ van Puijenbroek, E., de Vries, L. & Kant, A Trends in the use of anti-epileptic drugs during pregnancy in the Netherlands. Oct-2014 In : Pharmacoepidemiology and Drug Safety. 23, S1, p. 306-307

⁷⁷ Murphy S1, Bennett K2, Doherty CP, 2016 Prescribing trends for sodium valproate in Ireland. Seizure. Mar; 36:44-8

already observed between 2008 and 2013 while the use of valproate increased for other indications including BP. The IMS data did not clearly show decreasing trend in the period before.

The data from CNAMTS (FR), CPRD (UK) and Nivel (NL) also provided drug utilisation data for other medications prescribed in WCBP for epilepsy and BP. These data showed that next to the decreasing trend in valproate use in WCBP, there was an increase in the use of alternative products.

The data from the joint DUS are limited, as the study is ongoing and the small sample size for indication specific data in the post-referral period limits reliable conclusions. However, the preliminary data suggest that there is no evidence of improved prescribing behaviour after implementation of the RMM, as the proportion of WCBP in whom the prescribers considered other drugs before initiating treatment with valproate did not increase in the post-implementation period. However, no firm conclusions can be drawn yet since the study is ongoing, and only a limited period is included in the post-implementation period. The data from the joint HCP survey indicate that there is room for improvement regarding the knowledge and behaviour of the prescribers regarding the prescribing conditions of valproate in women of child bearing potential.

Therefore, PRAC considers that the currently available routine and additional risk minimisation measures to avoid exposure to valproate during pregnancy need to be further improved. The PRAC recommendations regarding these measures including the product information, the pregnancy prevention programme, the educational materials for HCPs and patients are provided in following sections of this report.

2.5.3. Switch or discontinuation of treatment

The PRAC reviewed available knowledge regarding discontinuation or switching of valproate before and during pregnancy and discussed this thoroughly during the consultations with experts.

2.5.3.1. Drug utilisation and post-marketing spontaneous data on switching or discontinuation

The limited drug utilisation and spontaneous data on pregnancy suggest that switching to alternative treatment or discontinuation of valproate therapy during pregnancy is more often done for patients with BP than for epilepsy patients. Further, the data suggest that the exposure to valproate during pregnancy is mainly limited to the first trimester of pregnancy in BP, while women with indication of epilepsy seem to be using valproate during longer periods during pregnancy. This suggests that the need for valproate therapy during pregnancy might be different for epilepsy and BP.

Currently available recommendations regarding switching or discontinuation are very limited:

Epilepsy

The Task Force of the European Academy of Neurology (EAN) provide a recommendation regarding switching of valproate in WCBP, which is based on expert opinion. According to this recommendation, the switch of valproate to an alternative treatment will commonly occur over at least 2-3 months: the new medication is usually introduced as add-on to valproate until a potentially effective dose of the second drug has been achieved and after this, an attempt can be made to gradually taper down and discontinue valproate. No specific recommendations are available regarding switching of valproate

during pregnancy. It is acknowledged that switching from valproate during pregnancy is a very challenging clinical issue and discontinuation during pregnancy might not be possible.

Bipolar disorders

No specific recommendations are available regarding switching valproate in patients with diagnosis of bipolar disorder, based on the available general recommendation regarding discontinuation of mood stabilisers in women with bipolar disorder, allowing sufficient time for a gradual discontinuation and close monitoring of the patients for possible relapse seem to be also relevant for discontinuation of valproate.

2.5.3.2. Need to identify best practices regarding switching or discontinuation of valproate

The available recommendations regarding the switching or discontinuation of valproate described in the previous section above, have been also discussed with clinical experts in consultation meetings as part of the current procedure. It has been agreed that the currently available recommendations provide limited information for switching or discontinuation in clinical practice. To obtain more robust information on the switching and discontinuation of valproate, the PRAC concluded that there is a need for a clinical study.

One of the MAHs (Sanofi) discussed the possibility to conduct a retrospective study to evaluate valproate treatment patterns, such as switching or discontinuation (as a categorical outcome defined at a specific time point or as a time-to-event analysis), in women who use valproate for the first time (incident users, with no prior history of valproate use) aged 14–49 years old and by indication in Europe. The PRAC agrees with this approach. Considering the estimated low prevalence of (drug resistant) types of epilepsy where valproate may be the only choice as well as the current valproate usage data, it is assumed that some WCBP (e.g. WCBP with focal epilepsy may switch in the near future from valproate to another medication. Increased awareness about risks of valproate, the implementation of contraindication and pregnancy prevention programme, etc. as well as the experiences from clinical practice from such cases may provide valuable information on the process and outcomes of switching. Also for bipolar disorder indication, some WCBP using valproate may stop using it or be switched to another medication, and the experiences from clinical practice might provide helpful insight to identify the best practices for discontinuation or switch of valproate also in this indication.

The MAH proposed to conduct this retrospective study using the CPRD database in UK, as the number of WCBP exposure to valproate in UK is highest in the European Union, which is endorsed. The MAHs are advised to also explore the feasibility of using databases in France, as for the bipolar disorder indication, the number of valproate prescriptions in WCBP was the highest in France according to IMS data. The MAHs should explore the possibilities of obtaining clinical data necessary to identify the successful/ best switching and discontinuation practices, e.g. the time period of switching or discontinuation process, the dosing scheme used in this period, details regarding the introduction of alternative treatment options in case of switching (timing, dosing, duration), relevant drug-drug interactions (e.g. oral contraceptives) the worsening of the diseases (e.g. seizures).

The PRAC considered that the study aimed at defining best practice when discontinuing, or switching from valproate should stratify patients using all relevant factors in both indications. For example, several characteristics need to be considered, patient characteristics: age, comorbidities (e.g., psychiatric comorbidities), the risk of drug–drug interactions with concomitant medication(s), seizure characteristics: EEG characteristics, clinical presentation, frequency, severity of seizures, epilepsy type: focal, generalized, combined generalized and focal, unknown, aetiology: structural, genetic,

infectious, metabolic, immune, unknown, previous AEDs: response and tolerance to the previous AEDs and finally in case of switching, the properties of the AED that is being initiated. The endpoints to define successful switching practices could include the proportion of patients remaining seizure-free, reduction of seizures or treatment tolerance. Furthermore, an appropriate follow-up period after switching or discontinuing treatment needs to be defined.

In addition, ethical aspects of such a study must also be considered. An alternative study design could be to examine discontinuing or switching valproate therapy in non-treatment-refractory males with epilepsy. However, such an approach could only be justified in male patients whose treatment is being switched or discontinued for medical reasons. In addition, it may not be possible to extrapolate the results of a study of non-treatment-refractory males with epilepsy to WCBP with treatment-refractory epilepsy given the differences in the characteristics of their conditions and possible treatment options. The possibility of studying the switching or discontinuation process of valproate in male patients with epilepsy or bipolar disorder and extrapolating the results to female population is not desirable, as PRAC considers that this approach may not be the best option due to the differences with regard to a number of important clinical characteristics between females and males that are relevant the switching process and may limit the generalisability of the results.

The PRAC strongly supported that the data obtained from the planned retrospective study are shared with EU experts in epilepsy and in bipolar disorder to adjust the expert consensus guidelines in terms of recommendations for discontinuation and switching of valproate in both epilepsy and bipolar disorder.

2.5.4. Analysis of data on visual reminder on the outer packaging

In some member states (e.g. Belgium, France), a pictogram and a text warning message on the outer boxes of valproate-containing products have already been implemented.

To define the best pictogram, an international user study was initiated by one of the MAHs (Sanofi) to collect data about the interpretation, preferences and acceptability of samples of pictograms and accompanying warning texts from a defined target group of potential users. 190 respondents from 19 countries (worldwide, 10 persons *per* country) participated in this study, and the majority was of the opinion that the pictogram tested (a pregnant woman crossed out) was the most understood and intuitive image (54% correct answers). It was also the most preferred pictogram (91% of participants) when taking into account the accompanying warning text and also the pictogram which best matched the warning text (84% of participants).

However during this procedure, and the public hearing held, the interventions voiced strong support for a visual reminder of the risks related to exposure during pregnancy on the outer packaging of valproate medicines. Further, patients in countries where a pictogram has been implemented provided positive feedback (notwithstanding that generics do not have yet the pictogram to date).

Also during the HCPs, Patients organisations, patients and families (Stakeholders) meeting held in this review, all participants found the pictogram/symbol as adopted in France useful but the text should be added to make the information better understandable, and to avoid any interruption to the treatment without medical supervision. They supported that all MAHs should include the visual reminder (e.g. pictogram/symbol/warning) at the outer packaging, including the MAHs of generics. It was also highlighted that a visual reminder can be useful for patients with literacy and memory problems, and can be an additional trigger to initiate and support discussions between the patient and the pharmacist during dispensing. Any symbol chosen needs to be user-tested, as cultural differences may affect the

understanding of the symbol. The visual reminder/symbol should be supportive of, not replacing, all additional information to be given to women.

The PRAC also consulted the Working group on Quality Review of Documents (QRD) of the EMA which provided the following feed-back on the proposed pictogram by the MAH (Sanofi).

The pictogram proposed can easily be misinterpreted and was not supported by robust data; 54% only of correct positive results for the user test reflect a poor comprehension level. The preference of the group was the inclusion of a box warning rather than a pictogram, similarly to what has been implemented for other teratogenic medicinal products (e.g. thalidomide). There was a consensus among the group on the fact that there is a clear need to attempt to find some common grounds on which a pictogram could be accepted for a centralised product with an explanatory text which can then be applied in all MSs. The text must be clear and in line with the product information. The group acknowledged the difficulty in finding a single pictogram for all EU Member States and for all teratogenic/ foetotoxic medicinal products; in particular the group noted the complexity of differentiating through a symbol, cases where the product is contraindicated versus cases where the product has a warning in the product information.

This Working group also considered that the use of the pictogram alone could lead to a misinterpretation of its meaning, as it was shown by the user testing of the MAH. It is therefore recommended that the pictogram is accompanied by warning text.

The PRAC acknowledged the request from patients and HCP at the public hearing and stakeholder meeting for a visual reminder (symbol/pictogram) on the outer package of all valproate-containing products to emphasise the risk of valproate, the need for contraceptive measures and the need to contact the physician at time of pregnancy planning and once a patient has become pregnant.

The PRAC also reviewed several studies in the published literature comparing the choice of different pictograms regarding teratogenic risks as evaluated by patients. The study by You and colleagues (2011)⁷⁸ compared text only warnings on outer packaging with a warning including both text and a symbol and concluded that the latter, i.e. combination of text with a symbol was significantly better understood and correctly interpreted by patients than text alone warnings. This study was conducted in US among 500 primary care patients including patients with marginal and low health literacy scores, and the patients answers were analysed by three independent researchers.

Another study (Meyhor & Goldsworthy, 2009)⁷⁹ also conducted in US, highlighted that a carefully chosen, valid text alone warnings on the outer packaging may be also well understood by the patients, however a 'text only' warning on the outer packaging without a symbol may not be noticed and read by the majority of the patients, as shown in this study. In addition, this study showed that some symbols may be correctly interpreted also without text and that priority should be given to such symbols. However, the combination of a symbol and a text was the best understood and noticed type of warning on the outer packaging also in this study.

The PRAC also discussed whether such visual reminder should be also printed on the primary packaging (blister) but this would not be feasible for space reasons. For this reason, the PRAC does not recommend adding further information on the blister. Nevertheless, further consideration should be given to the possibilities of printing a short text warning on the blister for all valproate-containing products.

⁷⁸ You W.B., Grobman W., Davis T., Curtis L.M., Bailey S.B., Wolf M. Improving pregnancy drug warnings to promote patient comprehension. *American Journal of Obstetrics and Gynecology*. 2011 Apr; 204(4): 318.e1-318.e5

⁷⁹ Mayhorn CB, Goldsworthy RC. New and improved: the role of text augmentation and the application of response interpretation standards (coding schemes) in a final iteration of birth defects warnings development. *Birth Defects Res A Clin Mol Teratol*. 2009 Oct; 85(10):864-71.

In conclusion, having considered the pictograms and text warnings already implemented on the outer packaging in some EU Member States, the feedback received from the public hearing, the stakeholders meeting and the QRD group discussion, the PRAC requests the implementation of a visual reminder on the outer package of all valproate containing products.

This visual reminder should at the minimum include a text warning conveying the following messages: the medicine can seriously harm the unborn baby; an effective contraception is continuously needed when using the medicinal product; to contact immediately a physician in case of suspected pregnancy, intent of pregnancy or pregnancy; the treatment must not be stopped without medical supervision.

These messages can be materialised as follows:

This medicine can seriously harm an unborn baby.

Always use effective contraception during treatment with <invented name>.

If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.

Do not stop <invented name> unless your doctor tells you to.

This text reflects the minimum core concepts that should be included in the boxed warning / visual reminder in all Member States. These core concepts are in line with the boxed warnings already implemented in some Member States.

The decision to implement a symbol/pictogram on the outer package in addition to the minimum visual text reminder (as above), and its graphic content should be taken at national level, considering cultural differences and national preferences on the implementation of symbol (pictogram) and input from local patient representatives.

In view of the available evidence from studies conducted specifically to test pregnancy warnings on medication packaging, the PRAC recommends a combination of a validated text and symbol for the visual reminder to be mentioned on the outer packaging for valproate and related substances. Indeed, such combined pictogram is better noticed and understood by the patients.

The visual reminder should be user tested nationally and agreed with the national competent authorities in each of the Member States. Any differences of understanding arising from the national user testing will need to be taken into consideration to define the most optimal visual reminder in each territory.

3. Expert consultation and Stakeholders input

The PRAC requested several consultations with different stakeholders during this review in order to collect all the available current information from different sources. This was also to see whether additional measures were implemented in MSs but also to receive feedback from stakeholders.

3.1. Written consultations

- Member states

The PRAC requested to all MSs at the start of the review to confirm all their later info (via a Non-urgent information request) on the current awareness of healthcare professionals on the risks of using

valproate during pregnancy and in WCBP, and any other data on the implementation of the risk minimisation activities and their effectiveness, following the 2014 referral on valproate. The MSs have confirmed whether the RMM from the previous review were implemented, as well any other additional measures that they might have taken at national level. For example some MSs have implemented a Patient card and/ or a pictogram already in their territory. In addition the results of national studies also were also submitted. These were summarised in previous sections of the report.

- Healthcare professionals and patients organisations

The PRAC also requested to stakeholders, (HCP associations and Patients) at the start of the review to request info on their current awareness on the risks of using valproate during pregnancy and in WCBP, and also the experience of the implementation of the risk minimisation activities following the 2014 referral on valproate. The results of different surveys were submitted to PRAC, giving additional information on the knowledge and on the real life information and experience. These results were also summarised in previous sections of the report.

3.2. Public hearing

The PRAC requested that a public hearing be held on 26 September 2017 inviting the general public to present to the PRAC their experience, their awareness, and also any suggestions to improve the awareness and minimise the risks.

The information obtained during the public hearing was duly considered by PRAC in this assessment. Issues raised during the public hearing such as the need for evidence and a better clinical guidance regarding the discontinuation or switching of valproate, the strong support for a visual reminder of the risks related to exposure during pregnancy on the outer packaging of valproate medicines, the need to investigate the impact of valproate use in males on pregnancy outcomes, the need for registers on valproate use and pregnancy outcomes are discussed in the assessment report.

In addition, several issues on the role of the HCP, their coordination and the organisation of the healthcare system were raised that need to be addressed at a national level by the healthcare professionals organisations and public health authorities.

In particular, more coordinated care services at national levels, to ensure individualised care plans for those affected (with consultation groups, channels, multimedia) were mentioned.

Involvement of learned societies, healthcare and patient organisations are particularly important to ensure appropriate awareness of the risks and effectiveness of the measures to minimise the risks. Family planning clinics may also play a role in the dissemination of information at national level. Reminders of the need to ensure that every time valproate is dispensed women should receive it in appropriate packaging accompanied by information on the risks. The role of the pharmacist could be enhanced, as well as measures for pharmacists to convey the information at time of dispensation.

Furthermore, alert prompts should be embedded in prescribing and dispensing software, to ensure flagging to the HCP the risks and the need for a discussion with patients. These should be flagged with clear instructions to HCP at the point of care (this would be optimal if linked to patient records i.e. female vs. male patient, to ensure that caregivers were not swamped with inappropriate warnings).

Regular (e.g. annual) reviews for all women receiving long-term valproate, to ensure that their understanding of the risks and benefits was updated appropriately as their life plans change, and as it was highlighted that the epilepsy patient population may have memory issues. Age-appropriate information packages should be developed and distributed and re-assessment in teenage years should be performed.

A record that women had been appropriately counselled regarding valproate risks (what was given as information and when) was mentioned. Compulsory Patients cards should be considered and ensuring effectiveness of the information distribution should be performed.

National registers of women who were receiving valproate, and children who had been exposed to valproate during pregnancy should be considered.

It was noted that promoting electronic patients records and its use to better target the information and register compliance might be of value.

Further development of professional education (pharmacists, specialists, general practitioners but also, paediatricians, nurses and midwives) in particular continuous training along the professional life, so that all healthcare professionals are adequately aware of the risks associated with valproate use in pregnancy was suggested. The risk of withdrawal of the medicine should be clearly highlighted as well as therapeutic guidelines should be developed on how to withdraw or to replace valproate for a patient. Especially for bipolar patients the decision on valproate use should be by a multidisciplinary team, including psychiatrists trained on valproate, midwives and gynaecologists.

Public awareness campaigns were considered as important measure to communicate on the matter. It was suggested to put in place national helplines, frequently asked questions (FAQs) and material distribution in surgeries and clinics. There is a need to use the scientific community as channels for the dissemination on the use of valproate in pregnancy and its risks. The information should be included in scientific journals and collaboration between learned societies should be sought to disseminate the message. Therapeutic guidelines are an important document to provide adequate information to the prescriber.

Based on the information received during the public hearing, additional questions on the characterisation and minimisation of the risks following the public hearing have been addressed to the stakeholders for the face-to face meeting and to the MAHs.

3.3. Healthcare professionals, patients' organisations and patients, families and carers meeting

Following the public hearing and the proposals to increase the awareness and minimisation of the risks, the PRAC wanted to further explore the suggestions with the Stakeholders (HCP, and patients) in order to have practical recommendations on what RMM may be adequate and feasible to be implemented. A summary of the discussion at the meeting is presented below.

The PRAC requested the view of the stakeholders on the best source of information for patients regarding the risks of valproate if taken during pregnancy, and the timely provision of this information.

It was supported by all participants that personal communication and trust with the HCP should be the base of the communication, with positive messages and explanations.

Personalised age-appropriate information (and tailored language) is important to reach the woman at different stages of her life. Different routes can be employed (electronic, hard copies, social media etc.).

The role of pharmacists was also highlighted in the discussion as very important and relevant in the distribution of the information.

Following treatment initiation, annual reviews of treatment by specialists (neurologists/psychiatrist) should take place for all women of childbearing age, and treatment options should be discussed with

them, and should take into account the particularities of each indication (epilepsy/bipolar disorder). The treating dose should also be monitored and adapted (as needed) in these annual reviews.

Information on the use of all anti-epileptic drugs (AEDs) during pregnancy should be discussed. The risks of the treatment options should also be provided at the appropriate time.

Pregnancy prevention plan (PPP) and monthly pregnancy tests in the case of chronic syndromes as epilepsy required careful and specific consideration were also discussed. Pregnancy support and counselling plan should be in place and tailored to specific situations.

All participants agree that additional restrictions of use of valproate in pregnancy should be considered, but it needs to be carefully balanced with the need to keep access in certain cases, as valproate remains a valid treatment to many women.

The role of the specialists was emphasised, not only neurologists and psychiatrists but also the participants identified other specialities which also need to play a role in the prescription and delivering the information to women.

As the efficacy of contraceptive pills may be affected by concomitant medication taken in addition to valproate alternative contraception methods should be used; educational material on contraceptive methods can be used as another way to spread the information on the risks of valproate during pregnancy. Contraception methods should be included in the treatment guidelines when valproate is used.

In case of pregnancy while on valproate use, a planned procedure of counselling should be organised with the woman and her partner. Midwives play an important role on postpartum and breastfeeding care and generally during the perinatal period.

The responsibility of National Authorities to deliver consistent information and materials to all HCPs in a no branded fashion was also emphasised.

The switching to alternative medications should be part of the annual treatment review of the patient and all the options should be made available to her. The partner/guardian/carer should be involved in these discussions as relevant. Other considerations should be discussed with the woman (e.g. the temporarily limitations in driving) so she makes an informed decision. Different healthcare systems in several countries have limited alternative reimbursed treatment options and this may hinder the switching procedure. This limitation has however to be seen in the light of the consequences for the family and affected children, on woman's career and consequences of caring for special needs children.

Awareness of the risks is vital. Consistency of information is crucial especially in the representation of the risk to the patients. For women having valproate as their only possibility of effective treatment, adequate support to discuss alternative parenting options should be in place. The information needs to be available in all EU languages.

Learned Societies can undertake surveys to check overall awareness and availability of national guidelines. Whilst these surveys may be international and involve a significant number of patients, they have some limitations that need to be taken into consideration (e.g. selection bias). Inventory of treatment guidelines may also be useful. In view of its audience, Wikipedia updates may be one of the ways the information can be made available and the Learned Societies can play an important role in making sure that information posted is regularly revised according to the latest scientific knowledge. Professional educational programmes on pharmacovigilance issues should be organised regularly by also involving the national authorities.

The patient organisations can play a key role if information is available to their members but at the same time the difficulties to convey information in patients in some Member States due to the lack of epilepsy associations were mentioned.

HCPs can facilitate the awareness and some HCPs, like midwives, can actively advise women on pre- and post- conception, breast-feeding, and ensure the timely contact with women organisations to make an impact.

Surveys need to take place periodically with HCPs to first assess the awareness but also to re-evaluate whether the information is kept updated. Additional research is needed on the HCPs continuous knowledge, involvement and adherence. Information should be collected on the number of initial prescriptions, switches/discontinuation and long-term treatments. Qualitative studies in combination with epidemiological studies are required. Research in healthcare knowledge and awareness should go beyond established organisations; the impact generated should be measurable now and in the future, for example as change in prescribing practise.

Register(s) on epilepsy and valproate, including mothers and affected children, may also provide useful information. All antiepileptic drug (AED) registers should be set up to understand the risks to the other anti-epileptics drugs as well as valproate.

In addition, there were questions raised regarding the scientific knowledge on the effect of valproate to the offspring when the father is treated and in the third generation offspring.

The PRAC duly took note all the interventions of the participants and took them into consideration in the recommendation of this European review.

3.4. Scientific advisory group on Neurology

The PRAC in order to get more information on the clinical use of valproate in the indication of epilepsy, requested to the SAG Neurology to identify whether there is a patient population that can be identified where the benefits outweigh the risks in the treatment of epilepsy for valproate use in pregnancy and women of child bearing potential (WCBP) not using effective contraception. The SAG Neurology concluded that for focal epilepsies, there are a number of alternatives to valproate with either superior or similar efficacy, and valproate should not be initiated as a first-line treatment.

For a very small proportion of genetic generalised epilepsy (GGE) about 20% of GGE patients are drug resistant/have refractory seizures became seizure free with valproate (Gesche et al, 2017)⁶⁵.

There are specific epileptic syndromes where valproate remains the most appropriate treatment as presented by Tomson and colleagues (2015)⁶⁶. The SAG Neurology also confirmed that where an initiation of valproate is considered in female children and WCBP, the decision must be taken and treatment monitoring performed by a specialist (neurologist, neuro-paediatrician) experienced in the treatment and diagnosis of epilepsy. All efforts should be made to regularly re-evaluate the need of continuing VPA treatment in female children and WCBP.

In that respect it was an agreement that a contraindication in the treatment of epilepsy in all female patients of childbearing age would indeed hinder the optimal treatment of some epileptic patients it was not supported by the SAG experts.

In the cases for which it is ascertained that valproate is the only available option, the risk of generalised tonic-clonic seizures (GTCS) and sudden death from epilepsy (SUDEP) weights against the replacement/withdrawal with different AEDs. In other cases, alternatives (such as lamotrigine or leviteracetam) may be considered as safer options, which seem to have the lowest risk of overall malformation. The current data show that that there are still some prescribers that do not comply with

the restricted use of the valproate in pregnant women and WCBP, and some SAG experts suggested that a stronger wording not to prescribe valproate to WCBP not using effective contraception and pregnant women could be considered.

The PRAC asked also the SAG experts on the best way to discontinue valproate when necessary. The SAG experts were unanimous in that there could be a disadvantage to discontinue /switch valproate during pregnancy. In other situations, current Guideline (EAN, ILAE) recommendations consider that the valproate withdrawal should be undertaken gradually (over weeks to months), but there is no evidence that could be used to recommend a specific scheme for either switch or discontinuation of valproate. Firstly, new treatment should be gradually introduced as add-on to valproate and secondly the progressive discontinuation of valproate can take place.

In the case of female children and WCBP a substitution early in life is recommended because this guarantees fewer difficulties (e.g. related to life choices, effects on career etc.) and less disruption of the quality of life. The experts supported the view that valproate treatment decisions must involve the patients/the carer and include a very clear communication of the risks and potential consequences to them. In patients planning pregnancy a discussion about switching valproate for another treatment, and highlighting the risks of the alternatives. For pregnant women on valproate, the experts stressed the risk of loss of seizure control may have severe maternal or foetal consequences, including death (SUDEP). The experts acknowledged the differences among the EU MSs pertaining to the treatment recommendation guidelines, dosages used, use of folates, and even ways of prescribing the medication.

3.5. Scientific advisory group on Psychiatry

The PRAC also consulted the SAG Psychiatry regarding the place of valproate in the treatment armamentarium for patients with bipolar disorder in clinical practice and whether there is a difference in the need for valproate with regard to the treatment of mania as compared to the maintenance after a patient treated for mania has responded to valproate. The experts were of the opinion that there is some place for valproate in bipolar disorder but not as first-line treatment. No difference in the need for valproate between the acute and the maintenance treatment phases was identified. As an additional comment, the experts pointed out that in recent years strong evidence indicated that lithium has lower reproductive toxicity than originally thought. Lithium is recommended as first-line treatment in many therapeutic guidelines, but it is still perceived in a negative manner due to its safety profile and subsequent requirements for close monitoring.

The experts could not identify a sub-population within the pregnant and WCBP bipolar patients where the benefits of valproate would outweigh its substantial risks.

One issue that the experts highlighted was the difficulties of the definition of the effective contraception; advice from contraceptive specialists should be sought in that regard. Moreover, the experts emphasised also that adherence to the contraception is a crucial issue especially as bipolar patients in an acute manic phase are less likely to follow contraceptive advice requiring diligent (daily) adherence.

The experts considered that effective alternative treatments that can be used during pregnancy and also in WCBP are available (i.e. pharmacological treatments and Electroconvulsive therapy - ECT).

Regarding the discontinuation of valproate, the experts acknowledged that there are no specific recommendations for valproate switch / discontinuation and that the approach is based on clinical expertise. Some clinicians use the schedule recommended for the discontinuation for lithium as a

model since it is supported by scientific data over a few weeks. The experts also highlighted difficulty in the dosage adjustments of the valproate at the time of discontinuation or treatment replacement. In the case of a pregnant patient a much faster cross-tapering can be recommended while installing the alternative treatment.

Overall there are few scientific data on the comparative efficacy of valproate versus other drugs so that its place in the sequencing of treatments for bipolar disorder is uncertain. The panel agreed that high quality studies of the comparative efficacy of valproate and other treatments for bipolar disorder are urgently needed in order to address this important question.

3.6. Working group on Quality review of documents (QRD)

In the context of this EU review, PRAC asked questions to the Working group on QRD regarding the acceptability of the proposed pictogram (a pregnant woman within a red triangle), alternative designs, the user testing study that was performed by the MAH Sanofi, and the benefits from a single symbol/pictogram for all teratogenic and feototoxic medicinal products for all Member States. The summary of the recommendation of the group were presented in previous sections of this report.

4. Risk management

The Committee, having considered all the information and data submitted in the procedure proposed pharmacovigilance activities to further characterise the risks associated with valproate and related substances and risk minimisation measures to minimise *in utero* exposure to valproate. Below are presented all the activities/measures that PRAC recommends for the use of valproate in all indications.

4.1. Risk management plan

Considering the safety issues related to valproate and the ongoing and planned additional pharmacovigilance activities and risk minimisation measures, all MAHs are requested to have in place a risk management plan (RMP).

The RMP should include the risk of teratogenicity and the details and timelines of the ongoing and planned additional pharmacovigilance activities. The risks to unborn children *via* third generation and paternal exposure should be included as an important potential risk. The RMP should include the synopses of all planned PASS studies.

4.2. Pharmacovigilance activities

4.2.1. Non-clinical studies

The following studies should be conducted by the innovator MAH (Sanofi) only:

1. Ames test in addition to *in vitro* mouse lymphoma assay to indicate for the occurrence of both gene mutations and clastogenicity. Synopsis will be submitted together with the RMP.
2. Study the impact of valproate on the epigenome of male and female germ cells. A panel of experts may be consulted. Scientific advice may be sought by the MAH.

Protocols will be submitted to the competent authorities together with the RMP.

4.2.2. Non-interventional clinical studies

Several post-authorisation clinical imposed studies should be performed by all MAHs, and are presented here below.

In particular, the PRAC requested MAHs to perform a drug utilisation study to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate. The PRAC recommends the MAHs to continue the ongoing drug utilisation study and to amend the study design to include the updated conditions of use for valproate and related substances. Databases with existing data on pregnancy and contraception should be investigated.

In addition, the MAHs are requested to conduct an observational study to identify and evaluate the best practices for switching of valproate and related substances in clinical practice.

The MAHs are requested also to conduct a survey among HCP (including prescribers and pharmacists) to assess their knowledge and behaviour with regard to the pregnancy prevention programme as well as their receipt/use of DHPC and educational materials. In addition, the MAHs should perform a survey among patients to assess knowledge of the patients with regards to the pregnancy prevention programme as well as receipt/use of educational materials.

The MAHs are requested to conduct a PASS to further characterise the foetal anticonvulsant syndrome in children with valproate *in utero* exposure as compared to other anti-epileptic drugs. This study should be based on existing registries.

Furthermore, a retrospective observational study to investigate the association between paternal and transgenerational exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, should also be conducted by the MAHs.

The MAHs are strongly encouraged to collaborate and perform joint studies.

4.3. Risk minimisation measures

4.3.1. Amendments to the 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 further minimise the risks associated with valproate use during pregnancy. These changes include amendments to sections 4.2, 4.3, 4.4 and 4.6 of the summary of product characteristics (SmPC). Sections 2, 3 and 4 of the package leaflet (PL) will also be amended including the information of the boxed warning at start and the Quick response (QR) code.

For all indications (epilepsy, bipolar disorders and prophylaxis of migraine attacks), the PRAC considered that medicinal products with substances related to valproate should be contraindicated in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled. In the indication bipolar disorders and prophylaxis of migraine attacks valproate treatment is contraindicated in pregnancy. In the indication of epilepsy, valproate treatment is contraindicated for use during pregnancy unless there are no suitable treatment alternatives. Section 4.3 of the SmPC has been updated accordingly.

The SmPC should reflect that for female children and adolescents, women of childbearing potential and pregnant women, valproate treatment should be initiated and supervised by a specialist in the management of epilepsy.

The need for treatment should be annually reviewed by a specialist. 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 section 4.4 of the SmPC, the conditions of the pregnancy prevention programme are listed and described below.

In section 4.6 of the SmPC is also updated to reflect the newly introduced contraindications and recommendations in case of pregnancy and pregnancy planning.

When planning a pregnancy, the woman must consult a specialist experienced in the management of the disease and treatment with valproate should be discontinued and, if appropriate, switched to an alternative treatment prior to conception, and before contraception is discontinued. For the indication epilepsy, every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

In the outer packaging a visual reminder should be included informing that the product can harm the unborn child and that effective contraception should be used.

Quick response (QR) code on the package leaflet may be a helpful method to prompt patients directly to actual digital information. Educational materials for the patient which have been approved by the NCAs can be made available via QR code in accordance with national regulations and according to the CMDh position paper⁸⁰ on the use of QR codes to provide information about the medicinal product.

The MAHs should liaise with the national competent authorities to implement this measure.

The corresponding sections of the package leaflet were amended accordingly.

Pregnancy prevention programme

The PRAC recommended that the use of valproate in WCBP should be subject to stringent restrictions to prevent exposure during pregnancy in view of the teratogenicity and neurodevelopmental disorders due to valproate. In order to achieve this, the PRAC concluded that a pregnancy prevention programme (PPP) should be implemented.

The PPP will include the following conditions:

- Individual circumstances should be evaluated in each case involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.

⁸⁰ CMDh position paper on QR codes

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_313_2014_clean.pdf

- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the requirement to use effective contraception (for further details refer to subsection contraception of the boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders <or migraine>.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (annual risk acknowledgement form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Guidance and details on the conditions of the pregnancy prevention programme are reflected accordingly in the updated educational materials (HCP guide, patient guide, patient card and annual risk acknowledgement form).

4.3.2. Educational materials

Educational measures are necessary in order to ensure that HCPs 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 of exposure on valproate in pregnancy.

In the previous European review (2014), several educational measures were recommended. Nevertheless, as shown in the data reviewed in this procedure they did not reach sufficiently the targeted audience and did not lead to a significant impact on prescriptions.

The MAHs are strongly encouraged to collaborate and liaise with the NCA to develop a single version of each educational material and to coordinate to optimise the dissemination of the agreed educational materials.

For intravenous formulations only, the relevance of the additional RMMs and in particular the patient card and the annual risk acknowledgement form should be considered on a case-by-case basis.

The PRAC recommends that the following educational materials are part of the pregnancy prevention programme (PPP).

A guide for HCP

The PRAC requested the development of an improved HCP guide 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.

This guide should explain the pregnancy prevention programme and its conditions to be met. It should explain the requirements prior to starting treatment with valproate and modalities for annual re-assessment of the need for valproate therapy and discontinuation and switching to alternative treatment options in female children who experienced menarche and women of childbearing potential.

The HCP guide should include the recommendation to inform the parents of young girls using valproate about the need to contact their specialist once their daughter has experienced menarche.

Recommendations on switching or discontinuing valproate as well as recommendations on pregnancy planning should also be included aiming at providing this information to the patients.

The guide should also include the actions to mitigate the risks associated with the use of valproate in case of pregnancy.

This guide should allow prescribers to familiarise themselves with the more recent data on disorders of development in the exposed child, provide information about the risks of valproate monotherapy and poly-therapy and a description of the roles of different HCPs. It should also provide instructions to the prescribers on the distribution of the patient guide and the completion of the risk acknowledgment form.

The guide for prescribers should be read in conjunction with the summary of product characteristics.

The final version must be agreed with the National competent authorities in each Member State.

A patient guide

The PRAC requested the development of an improved guide for women who are being prescribed valproate and are able to get pregnant.

The guide should provide comprehensive information on risks to the unborn child due to *in utero* exposure to valproate and related substances, the details of the pregnancy prevention programme and the required actions in terms of pregnancy or intention to become pregnant. In order to provide adequate information, it should be tailored for different situations in the life-time of a woman and be age-appropriate: 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. Information in the annual risk acknowledgement form and the patient card should be mentioned.

This guide should be delivered to the patient as hard copy and electronic format.

The patient guide should be read in conjunction with the package leaflet.

The final version must be agreed with the National Competent Authorities in each Member State.

Patient Card

The patient card requirement was one of the risk minimisation measures that were implemented by some NCAs in addition to the measures adopted in the last European review (2014)⁸¹ and was well received by the patients and their families. The usefulness of the patient card has been emphasised during the public hearing and the stakeholders meeting.

81

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f

Having considered the above, the PRAC requested the patient card to be made available in all MSs and for all patients who receive valproate. Information on the patient card should be brief and concise regarding the efficacy of the medicinal product but also the harm to the unborn baby when taken during pregnancy. The use of effective contraception without interruption during the treatment with valproate should be included, as well as a reminder for annual re-assessment by a specialist. Advice to not discontinue the treatment as well as the need to contact the doctor when a pregnancy is planned should also be there.

This patient card should be attached at the outer carton to prompt the pharmacist to discuss with the patient the risk associated with valproate at the time of the dispensing. It was also identified that according to a survey conducted by the Pharmaceutical group of European Union (PGEU), the main barrier for implementation of risk minimisation measures at pharmacy level was that the materials would get lost in pharmacies. Having the patient card attached on the packaging will avoid such situations and will enable provision of the patient card to every patient when valproate is dispensed. Specific temporary measures regarding dissemination of the patient card until the patient card is attached to the outer package should be decided at national level taking into account the different role and organization of community pharmacies in the Member States.

The final version must be agreed with the national competent authorities in each Member State.

Annual risk acknowledgment form

The PRAC also requested that as part of the PPP an annual risk acknowledgment form should be made available in order to support the transmission of the information to the patient and support the dialogue between the prescriber and the patient to ensure that the patient has well understood this information.

This form should include a checklist for prescribers and patients or carers. This checklist is intended to be used at time of treatment initiation and annual review by physicians experienced in the management of epilepsy, bipolar and migraine to facilitate a discussion with girls and WCBP patients and/or their carers about the suitability of a treatment with valproate and its risks.

This acknowledgment form must cover the following aspects: information about the risk for the unborn baby to an *in utero* exposure to valproate or related substances; the need for negative pregnancy test at treatment initiation; the need of an effective contraception without interruption during the entire duration of treatment with valproate (if child bearing age); to contact her physician once she want to plan a pregnancy, and to ensure timely discussion and changing to alternative treatment options prior to conception, and before contraception is discontinued, the need to contact their doctor immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy.

The checklist should be used in conjunction with the summary of product characteristics and package leaflet.

The final version of the annual risk acknowledgment form must be agreed with the national competent authorities in each Member State. The requirements for signing of the form and archiving are subject to national law and will be defined during the national implementation.

4.3.3. Direct Healthcare Professional Communication and 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, school nurses, etc. The communication is to be sent in accordance with the agreed communication plan and together with the educational materials. The 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. The letter should cover all valproate containing products authorised in that Member State and all the indications authorised.

4.3.4. Improved distribution of educational materials and additional channels of communication

During the public hearing, it was highlighted that availability of electronic only educational materials should not replace printed educational materials. This was also concluded at the stakeholder meeting (including patients and HCPs) that electronic aids (on-line information applications - 'apps') can be useful and helpful especially for younger women; however these should be seen as complementary tool and not to replace standard (face-to-face) channels of communication.

HCPs may have different preferences on how they would like to receive the materials (digital or hard copy). Electronic distribution of educational materials to HCPs in addition to hard copies distribution is supported by the PRAC.

More involvement of pharmacists is supported by the PRAC in the communication and distribution of educational materials. The role of the pharmacists in the management of a chronic disease is fundamental, at start but also at subsequent dispensing. Patients require different support and information at different phases of their life. The role of the pharmacists is crucial to follow-up regularly the patient and to tailor the advice to individual patient's circumstances. This was also highlighted during the HCPs and patients meeting that the pharmacists should receive an adequate training on the risks, and conditions to deliver valproate-containing medicinal products and the information to provide to the patient.

Pop-up alerts in prescribing and pharmacy dispensing software to remind HCP about the risks of valproate and the need to re-evaluate the use of valproate in WCBP might be an effective strategy to reinforce the implementation of the risk minimisation measures and this is supported by the PRAC. In the HCPs and patients meeting, it became apparent that a software programme might also be helpful to approach patients in their different stages of their life (first prescription, at time of family planning, unintended pregnancy). Further collaboration between MAHs and NCAs to explore the possibilities of prescribing and pharmacy dispensing software (e.g. pop-up alerts, reminders) may be necessary to explore the possibilities at national level and is strongly encouraged by the PRAC.

Collaboration between patient and professional organisations and NCAs to develop additional channels to distribute information/educational materials such as web platforms to publish materials with cross-references to each webpage depending on national particularities should be further explored. During the HCP and patients (stakeholders) meeting it was emphasised that learned societies and patient

organisations can play an important role in making sure that information delivered is regularly revised according to the latest scientific knowledge.

Therefore, the NCAs in individual Member States are encouraged to facilitate the discussions with the learned societies, relevant professional health care organisations and patient organisations, or other appropriate organisations in Member States in order to:

- to enable update of the clinical treatment guidelines for epilepsy, bipolar disorder and migraine in the Member States where such guidelines exist (the latter is only relevant for Member States that have valproate-containing products with prophylaxis of migraine as indication);
- discuss the feasibility and enable implementation (where possible) of the conditions of PPP for valproate in electronic prescribing and dispensing (e.g. pop-ups/medication alerts);
- Ensure that the updated recommendations regarding the use of valproate in women of child bearing potential and pregnancy are incorporated in the curriculum of (continuous) medical education of HCPs.

It was strongly advocated at the public hearing and the discussions with patient organisations, patients and carers, to develop public campaigns to inform on the risks of valproate when used in pregnancy at Member State level. It is also very important to inform on the serious consequences for the woman and her baby when treatment is stopped spontaneously without physician supervision, especially for the epileptic patients. Thus, the Member States are encouraged to explore public campaigns, using different several channels of communication. These channels may include mass media campaigns, social media, visual displays (leaflets and posters) at relevant places (e.g. clinics, family planning centres).

4.3.5. Pack size and original packaging

During the public hearing, it appeared that patients do not always receive their medicines within the original package or with adequate patient information.

It is reminded that any medication dispensed to patients should be dispensed with the appropriate patient information and preferably in their original package. Having the original packaging, it helps the patients to better identify the medicinal product that they are taking, as the outer carton contains both the invented name and the name of the active substance. The PRAC discussed whether having smaller pack sizes available may improve the dispensing of information to the patients. Considering the current prescription / dispensing duration restrictions in some Member States, smaller pack sizes may facilitate dispensing of valproate in the original package. The PRAC noted that it may be challenging to have an adequate pack size for each patient in view of the highly individual dosing of valproate, which depends for instance on age, body weight, liver and kidney function. In view of the complexity of the dosing, the chronicity of the disease, smaller pack sizes is not expected to be an effective risk minimisation measure and might affect patient compliance in some situations. The MAHs are however recommended to reassess the adequacy of their pack sizes.

The PRAC recommended appropriate communication at national level to pharmacists to emphasise the importance for patients receiving adequate information i.e. patient leaflet and the patient card. If according to national practices, unpacking is necessary, the patients must receive all relevant information, including a patient leaflet.

4.3.6. Additional monitoring

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

5. Conclusions and Benefit-risk balance

In October 2014, following a referral procedure under Article 31 (EMA/H/A-31/1387), the PRAC concluded a review⁸² of all available data from pre-clinical and pharmacoepidemiological studies, published literature, spontaneous reports as well as the views of the relevant experts on the safety and efficacy of valproate and related substances in female children, women of childbearing potential and pregnant women. The review confirmed 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) showed that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29).

Data also showed that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. This risk seemed also to be dose-dependent but a threshold dose for which no risk exists could not be established. The exact gestational period at risk for these effects was uncertain and the possibility of a risk throughout the entire pregnancy could not be excluded. Studies in preschool children exposed *in utero* to valproate showed that up to 40% experience delays in their early development such as talking and walking, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Based on this review the PRAC recommended in 2014 strengthening of the restrictions on the use of medicines with substances related to valproate due to the risk of malformations and neurodevelopmental disorders in children exposed to valproate in the womb. The PRAC also recommended educational materials and communication to the healthcare professionals to appropriately inform on the risk of harm. In addition, survey of health care providers and a drug utilisation study was requested in order to assess whether the PRAC recommendations were adhered to.

In view of lack of sufficient adherence with the abovementioned measures, France triggered on 08 March 2017 a procedure under Article 31 of Directive 2001/83/EC, and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of medicinal products containing substances related to valproate and issue a recommendation on whether the marketing authorisation(s) of these products should be maintained, varied, suspended or revoked.

In the course of the consultations that PRAC had in this procedure, some additional concerns have arisen, other than the well-known and documented harm to the foetus during *in utero* exposure. The potential impact of paternal use of valproate, the potential effect on the third generation offspring and the potential effects on mitochondria (mitochondrial toxicity) were discussed.

Regarding exposure via seminal fluid, estimation was made of the area under curve (AUC) for valproate in a woman following vaginal exposure to valproate via seminal fluid of a man treated with valproate. This resulted in a value which was more than 25,000 times lower than the AUC in a woman treated orally with an equal dose (single oral dose 500 mg). It can be concluded that it is extremely

⁸² Valproate 2014
(http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WCOb01ac05805c516f)

unlikely that valproate, when used by a male patient, could cause adverse effects to the embryo/foetus by this route. The PRAC requested the conduct of a retrospective observational study to further characterise this theoretical risk.

Genetic changes can be divided in gene mutations and chromosome aberrations. It seems theoretically possible that gene mutations in sperm cells could be transmitted to the offspring. However, tests for gene mutations were negative. Therefore, this type of transmission is not likely to occur for valproate. The PRAC therefore recommends that other tests could be performed (e.g. *in vitro* mouse lymphoma assay) to further explore this hypothesis. Several tests for chromosome damage were positive. Severe chromosome damage is expected to lead to death of sperm cells / reduced fertility and not to transmission of mutations to the offspring. It is unknown whether slight chromosome damage might be transmitted to the offspring. Further investigation is recommended by PRAC.

The epigenetic mechanism refers to the possibility that changes in the gene expression in the gametes are transmitted to the gene expression in the embryo (for example by changes in DNA methylation). Theoretically this is possible by changes to the gene expression in sperm cells of adult males or by changes to the developing germ cells in the embryo. In one experiment it was shown that a change in gene expression (one gene) in male mice after exposure to a histone deacetylases (HDAC) inhibitor (not valproate) was observed also in the offspring of these mice (Jia et al, 2015)⁸³, so possible in principle. It was shown in a transgenerational experiment in mice that administration of valproate during pregnancy (day 10) produced autism-like symptoms and increased expression of several proteins in the brains up to the third generation offspring. This was not shown for teratogenic effects as malformations in the first generation offspring was not observed in the second and third generation offspring (Choi et al, 2016)⁸⁴. Although several limitations exist, the study suggests that there was some transgenerational effect. The PRAC agrees that more research is necessary to evaluate whether valproate indeed may induce transgenerational alterations of gene expression to the offspring and the types of consequent effects.

Furthermore, in a literature overview regarding effects on mitochondria, known side effects were described such as liver toxicity, Reye-like syndrome, pancreatitis and immune deficiency (leukopenia). There is no clear evidence that mitochondrial dysfunction caused by valproate is associated with the development of autism. The PRAC is of the opinion that the currently available data do not warrant further investigation regarding the potential association between mitochondrial dysfunction and autism.

In the previous European review (2014), several educational measures for patients and healthcare professionals (HCPs) were recommended. Nevertheless, as shown in the data reviewed in this procedure educational measures did not reach the targeted audience in a satisfactory rate in order to have any significant impact on prescriptions.

Usage data from the ongoing joint drug utilisation study (DUS) as well as other data (surveys, national surveys, anecdotal evidence etc.) that have been evaluated in the current referral indicate that valproate is still used by a considerable proportion of WCBP in different MSs for both epilepsy and bipolar disorder indications.

A wide consultation was done on the request of PRAC to gather all the latest information in terms of scientific and clinical knowledge with the consultation of two scientific groups (neurology and psychiatry), and to collect information from healthcare professionals, female patients themselves as well their families, from patient organisations (public hearing, stake holders meeting) who are

⁸³ Jia H, Morris CD, Williams RM, Loring JF, Thomas EA. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. *Proc Natl Acad Sci U S A*. 2015 Jan 6; 112(1):E56-64.

⁸⁴ Choi CS, Gonzales EL, Kim KC, Yang SM, Kim JW, Mabunga DF, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. *Sci Rep*. 2016 Nov 7;6:36250

advocating to better characterise and increase the awareness on the risk of harm to the foetus when using valproate during pregnancy. From these consultations it was evident that the specialists are aware of the risks discussed, but the information is not adequately reaching the patients timely and effectively.

In addition to the measures to increase awareness about risks of valproate, the different expert consultations provided clear recommendations to restrict the use of valproate. They also provided experience from clinical practice on the management of women who wish to become pregnant or are pregnant. In particular, experience from HCPs regarding the discontinuation of valproate or switch to other treatment was provided. To obtain additional robust information on the switch and discontinuation of valproate, the PRAC requested the conduct of an observational study to identify and evaluate the best practices for switching of valproate in clinical practice.

Regarding pregnancy/family planning in epilepsy, the PRAC also highlighted that, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

In view of the above, the PRAC recommended amendments to the product information, in particular to contraindicate its use to women of childbearing potential that fulfils the conditions of a pregnancy prevention program, and communication to healthcare professionals through a direct healthcare professional communication (DHPC). A pregnancy prevention programme will be implemented accordingly to prevent valproate exposure during pregnancy given that significant risk of lifelong harm is associated with its use. Educational 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 of exposure on valproate in pregnancy. The PRAC re-iterate that a single version of educational materials is disseminated, where appropriate. The MAHs are encouraged to collaborate and liaise with the national competent authorities to facilitate the dissemination of the agreed educational material.

The PRAC recommended the improvement of a HCP guide 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 requested that the patients are also informed about these risks appropriately. The guide should explain the pregnancy prevention programme and the conditions to be met prior to starting treatment with valproate. At least annual re-assessment of the need for valproate therapy and consideration of alternative treatment options in female children who experienced menarche and women of childbearing potential should be included. 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 guide and the risk acknowledgment form. The HCP guide should include the recommendation to inform the parents of young girls using valproate about the need to contact their specialist once their daughter has experienced menarche, information on need for switching when pregnancy planning, on the need to go through the risk acknowledgement form and the patient card, at least annually.

The PRAC recommended that a patient card to be made available in all MSs and for all patients who receive valproate. Information on the patient card should be brief and concise regarding the efficacy of the product but also the harm to an unborn child when taken during pregnancy. The use of effective contraception without interruption during the all course of treatment should be included as well as a reminder for annual re-assessment. Advice on non-interruption of treatment as well as the need to contact the doctor when a pregnancy is planned or suspected should also be included. This patient card

should be attached at the outer carton to prompt as a reminder the discussion between the pharmacist and the patient at the time of the product dispensing.

The PRAC recommended that the patient guide for female children, adolescents and women who are being prescribed valproate is further developed and improved. The patient guide should provide comprehensive information on risks to the unborn child due to *in utero* exposure to valproate and related substances, the details of the pregnancy prevention programme to avoid valproate exposure during pregnancy and the required actions in terms of pregnancy or intention to become pregnant. In order to provide adequate information, it should be tailored for different situations in the life-time of a woman and be age-appropriate: 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. This guide should be handed over to the patient.

The PRAC also reviewed the annual risk acknowledgement form which should be used and documented at initiation and during each annual review of valproate treatment by a specialist.

The PRAC taking into account all the evidence as well the areas where information is limited requested several measures in order to further characterise the risks, increase the awareness of the risks, restrict the use and measure the effectiveness of the currently proposed measures. The current ongoing drug utilisation study (DUS) should be adapted and continued to assess the effectiveness of the updated risk minimisation measures including the pregnancy prevention programme conditions and to further characterise the prescribing patterns for valproate. A survey among HCP to assess their knowledge and behaviour with regard to the new product information restrictions and whether they received the direct healthcare professional communication (DHPC) and educational materials, and another survey among patients to assess the receipt of the educational materials should be performed. A post-authorisation safety study (PASS) using data preferably from existing registries should be performed to further characterise the foetal anticonvulsant syndrome in children with valproate *in utero* exposure as compared to other anti-epileptic drugs. In addition in an effort to increase the knowledge on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, a retrospective observational study is recommended. Further, an observational study to evaluate and identify the best practice for discontinuation and switching of valproate treatment will be conducted.

The MAHs are strongly encouraged to collaborate on the requested measures and to perform joint studies.

Among the requests from the patients and family members who were consulted was the implementation of a visual reminder on the outer package to warn the women on the harm to the unborn baby and to also promptly advise them to use effective contraception. The PRAC agreed that such visual reminder on the outer carton is important to warn the patient on the risk and to prompt to consult a physician and requested the inclusion of a visual reminder on the outer packaging. In addition to the boxed text this may include a symbol/pictogram, with the details to be adapted at national level.

In view of the safety issues in discussion and the whole set of conditions for the risk minimisation aiming at minimising exposure in pregnancy, all MAHs need to have in place a risk management plan.

The medicinal products will continue to be listed in the additional monitoring list.

In view of all the above, the PRAC considers that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the agreed conditions to the

marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

6. Conditions to the marketing authorisations

The marketing authorisation holders shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

<p>A visual reminder on the outer package to warn patient about the harm to unborn baby and the need for effective contraception when using the medicinal product should be implemented in all medicinal products containing substances related to valproate.</p> <p>The details of the visual reminder should be agreed at national level and be subject to a user test taking into account input from local patient representatives.</p>	<p>Within 3 months after Commission decision</p>
<p>The MAHs of medicinal products with substances related to valproate shall perform a drug utilisation study to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate. MAHs are encouraged to extend the ongoing drug utilisation study (DUS).</p> <p>Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :</p> <p>The first interim report shall be submitted to the PRAC :</p> <p>Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years</p> <p>The final study report shall be submitted to the PRAC:</p>	<p>Within 6 months of the Commission decision.</p> <p>Within 12 months after endorsement of the study protocol.</p> <p>Within 48 months after endorsement of the study protocol</p>
<p>The MAHs of medicinal products with substances related to valproate shall develop and submit educational materials according to agreed core elements. These materials should ensure that prescriber are informed and the patients understand and acknowledge the risks associated with valproate in-utero exposure.</p> <p>These should be submitted to the National Competent Authorities:</p>	<p>Within 1 month of the Commission decision.</p>

<p>The MAHs of medicinal products with substances related to valproate shall conduct an observational study to evaluate and identify the best practices for switching of valproate in clinical practice.</p> <p>Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :</p> <p>The first interim report shall be submitted to the PRAC :</p> <p>Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years</p> <p>The final study report shall be submitted to the PRAC:</p>	<p>Within 6 months after Commission decision</p> <p>Within 12 months after endorsement of the study protocol.</p> <p>Within 48 months after endorsement of the study protocol</p>
<p>The MAHs of medicinal products with substances related to valproate shall perform a survey among HCP to assess knowledge of HCP and behaviour with regard to PPP as well as receipt/use of DHPC and educational materials.</p> <p>Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :</p> <p>The final study report shall be submitted to the PRAC:</p>	<p>Within 6 months of the Commission decision.</p> <p>Within 12 months after endorsement of the study protocol.</p>
<p>The MAHs of medicinal products with substances related to valproate shall perform a survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials.</p> <p>Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :</p> <p>The final study report shall be submitted to the PRAC:</p>	<p>Within 6 months of the Commission decision.</p> <p>Within 12 months after endorsement of the study protocol.</p>
<p>The MAHs of medicinal products with substances related to valproate shall conduct a PASS preferably based on existing registries to further characterise the foetal anticonvulsant syndrome in children with valproate <i>in utero</i> exposure as compared to other anti-epileptic drugs.</p> <p>Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :</p>	<p>Within 6 months after Commission decision</p>

<p>The first interim report shall be submitted to the PRAC :</p> <p>Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years</p> <p>The final study report shall be submitted to the PRAC:</p>	<p>Within 12 months after endorsement of the study protocol.</p> <p>Within 48 months after endorsement of the study protocol</p>
<p>The MAHs of medicinal products with substances related to valproate shall conduct a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring.</p> <p>Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :</p> <p>The first interim report shall be submitted to the PRAC :</p> <p>Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years</p> <p>The final study report shall be submitted to the PRAC:</p>	<p>Within 6 months after Commission decision</p> <p>Within 12 months after endorsement of the study protocol.</p> <p>Within 48 months after endorsement of the study protocol</p>
<p>All MAHs should have in place a Risk management plan (RMP).</p>	<p>Within 3 months after Commission decision</p>

With regards to the studies abovementioned, the MAHs are strongly encouraged to collaborate and perform joint studies.

7. Grounds for Recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing substances related to valproate.
- The PRAC considered the totality of the data submitted for valproate and related substances with regard to the teratogenic and neurodevelopmental risks, the use in clinical practice and the effectiveness of the risk minimisation measures in place. This included the responses

submitted by the marketing authorisation holders in writing as well as the outcomes of the scientific advisory groups in neurology and psychiatry. In addition, the PRAC considered the views of patient organisations, patients, families and carers, and the views of healthcare professionals in a public hearing and dedicated meeting.

- The PRAC confirmed the known risk of intra-uterine exposure to valproate and related substances, associated with an increased risk of developmental disorders and congenital anomalies in the offspring. No new significant information was identified regarding this risk.
- The PRAC concluded that the risk minimisation measures in place have not been sufficiently effective to prevent unintended *in utero* exposure to valproate and related substances in all indications.
- The PRAC concluded that the minimisation measures for medicinal products containing valproate or related substances should be strengthened through contraindication in all indications (epilepsy, bipolar disorders and prophylaxis of migraine) in women/girls of childbearing potential unless the conditions of the pregnancy prevention programme are complied with.
- The PRAC considered that the pregnancy prevention programme should reflect that in the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
- For their use in pregnancy for the treatment of epilepsy, the PRAC concluded that these medicinal products are contraindicated unless there is no suitable alternative treatment option. For their use in the treatment of bipolar disorders and prophylaxis of migraine these products are contraindicated in pregnancy.
- In addition, the PRAC recommended other changes to the product information such as warnings and precautions for use and updated information on the risks related to exposure during pregnancy to better inform the healthcare professionals and patients.
- The PRAC also concluded that there was a need to update the educational materials aimed to fully inform patients and healthcare professionals on the risks to the unborn child when exposed *in utero* to valproate, and to implement some further risk minimisation measures such as a visual reminder on the outer packaging, a patient card and an acknowledgment form to raise awareness about the risks and the need for contraception. PRAC also recommended post-authorisation studies to assess the effectiveness of the risk minimisation measures. Core elements of a direct healthcare professional communication were agreed, together with the timelines for its distribution.
- The PRAC also reviewed the available scientific evidence on the risk of malformations and neurodevelopmental disorders to offspring after paternal exposure, the risk of malformations and neurodevelopmental disorders to the third generation offspring and considered that further research is needed before conclusions can be drawn. The PRAC requested the conduct of post-authorisation studies.

In view of the above, the Committee considers that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the agreed conditions to the

marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for medicinal products containing substances related to valproate.

Appendix 1

Divergent position(s)

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

Procedure No: EMEA/H/A-31/1454

Medicinal products containing substances related to valproate

Divergent statement

We diverge on a single point of the PRAC recommendation. This is the statement which implies that counselling women where switching is not possible, without providing any quantification or qualification of such scenarios, will protect the unborn child from harm. We consider that it is unacceptable to create such an implication on the face of a regulated product's license in relation to use in the context of a planned pregnancy. Sodium valproate is a powerful teratogen. Children exposed in utero are at high risk of serious developmental disorders (up to 30-40% of cases) and/or congenital malformations (approx. 10% of cases). The regulatory responsibility is to avoid ambiguity on the benefit-risk profile of a medicine at the population level. In line with same, the PRAC agrees that a contraindication is warranted in women of child-bearing potential where conditions of the Pregnancy Prevention Programme are not met. Outside of same, any individualised considerations of informed consent should be at the level of the individual patient and their specialist(s) rather than a matter for the product license. It is not unique to this product that the right to self determination includes right to refuse treatment or select an alternative. Issues of informed consent are particularly complex in the context of the use of a medicine where the harm is to the unborn child. A generic reference to counselling as a sufficient measure for informed consent, on the face of the license, is inappropriate in a situation where there needs to be individualized decision making.

PRAC Members expressing a divergent opinion:

- Almath Spooner (IE)
- Julie Williams (UK)