



2 October 2017  
EMA/645752/2017  
Stakeholders and Communication Division

## Public hearing on valproate

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## **General public (patient representatives, carers, families)**

### ***Catherine Cox, Fetal Anti-Convulsant Support Association, UK***

I wish to represent the views of patients who have been prescribed Sodium Valproate in pregnancy resulting in a child born and subsequently diagnosed with the condition Fetal Valproate Syndrome. I am a patient previously prescribed the drug from the age of 16 years until the age of 30 years. I have one child with the condition and another not affected as I was prescribed Levetiracetam during my second pregnancy.

I wish to explain the lack of information which we still experienced by women prescribed Valproate and therefore the lack of choice they can have. I represent FACSA which is a support group dedicated to a campaign to provide information to women with epilepsy and better care for children affected by a Fetal Anti-Convulsant Syndrome.

All of my contributions will be factual, linked to evidence of the experiences of women and their affected children.

**Janet Williams, Independent Fetal Anti-Convulsant Trust (In-FACT) & FACS Syndrome Association, UK**

1) Sodium Valproate has been on the UK market since 1973 and during the 40 yrs a huge amount of research has been done which questions and shows the teratogenic ability of Valproate. In most cases we know that Valproate has a debilitating affect on the fetus causing life long impairments where constant supervision and care is required, especially once the parents are no longer able to provide such support. Due to the research over the past 4 yrs we know that around 30-40% affected have neurodevelopmental disorders with 11% having a major malformation. It seems that the tables have now turned for Valproate and that the risks now outweigh the benefits and so stronger measures are required on Valproate use.

2) The measures currently used to reduce the risk of Valproate in pregnancy have not been completed quick enough and the procedures to put the new warnings in place has been too long and too costly. Since the EMA became involved in 2014 around 1500 babies have been harmed with around 400 affected since the release of the toolkit in February 2016 in the UK. A more positive approach is definitely required.

3) It is imperative that the medical profession recognise that the relationship between Fetal Valproate Syndrome and Autistic Spectrum Disorders and ensure that a child with FVS receives a secondary diagnosis where possible to ensure the child also receives support with in the health and educational services. More emphasis is also required to raise the perception of Valproate and its dangers in all aspects with more research needed for the future and the approach to those dangers. Constantly there is new research on this topic which calls for a more in depth follow up by the Dept of Health in the UK especially following the decision of the French Government to banned the drug for the use in Bipolar

**Marine Martin, Association of Parents of Children with the syndrome anticonvulsant (APESAC), France**

I am Marine Martin, President of APESAC and I represent the French victims.

It's 4989 (four thousand nine hundred and eighty-nine) victims who contacted APESAC after being informed by TV in many interviews.

The situation remains extremely difficult for the victims:

- Sanofi refuses to acknowledge its responsibility and accuses the French health agency.
- Doctors say the proportions of victims given by the EMA studies are wrong.
- Since 2012 (two thousand twelve), 1500 (One thousand and five hundred) families have launched legal proceedings in civil, criminal, administrative and class actions. We have been lobbying the French government in order to obtain a public inquiry from the health general inspection (IGAS). The report shows the responsibility of Sanofi and public authorities. SANOFI did not put its drugs leaflets in conformity with the scientific knowledge of the moment.
- In September 2016 (two thousand sixteen) we eventually obtained a judicial investigation from the Paris public prosecutor's office after more than a year waiting.
- We demanded that SANOFI provide us the Periodic safety update report. We managed to obtain some of them and realized that since the beginning of its marketing, SANOFI knew the toxicity of valproate because many cases were reported to him.
- In March 2016 (two thousand sixteen), I was received by the Health Minister.
- I asked her to order studies to find out the number of victims of valproate. At the end, she presented me the first results of the investigation:
  - 14322 (fourteen thousand three hundred and twenty-two) women were pregnant and taking valproate between 2007 (two thousand and seven) and 2014 (two thousand and fourteen).
  - Only 8701 (eight thousand seven hundred and one) children were born alive.

These figures are huge because they highlight the number of pregnancies that haven't been able to go to term because of valproate!

I also negotiated the setting up of a compensation fund. This fund is in place since the first of June 2017 (two thousand and seventeen).

- In November 2016 (two thousand and sixteen), we drafted a National Diagnosis and Care Protocol with heads of genetics. This document explains the clinical picture of Foetal valproate Syndrome. But its writing has highlighted the doctors' misunderstanding of the pathology and the refusal from most of them to make the diagnosis, in fear of retaliation.
- In February 2017 (two thousand and seventeen): An audit of Parisian hospitals revealed an edifying observation:

Paris doctors are not aware of the new recommendations issued by the EMA.

I quote: "The major lack of information by Paris' Hospital doctors on the new prescription conditions for valproate results from multiple malfunctions at all levels. At Paris' Hospital, whether it is central or local, the multiplicity of actors in charge of regulating the subject of the drug and the safety of the

circuit and care revealed an inability to ensure a rapid and effective control of such a subject without real operational coordination."

- March 2017 (two thousand and seventeen) after months of negotiation I finally found an agreement with the government and the French medicines agency on the new logo finally available with the mention:

DEPAKINE + (plus) PREGNANCY = (equals) DANGER for epileptics and DEPAKOTE + PREGNANCY = PROHIBITED for bi-polars, and so that SANOFI does not change anything we passed a decree making this logo compulsory in its size and in its colour.

- In June 2017 (two thousand seventeen) we obtained the contraindication of valproate given to bi-polar women, because there are therapeutic alternatives for this disease.

Today we ask: prohibition of Valproate for migraine and bi-polarity. It is abnormal that the French recommendations are not extended to all Europe. Valproate is dangerous, and not only for the French!

In 2014 (two thousand fourteen), EMA explained that it seemed difficult to impose a pictogram of danger on sodium valproate drugs. The European regulation on drug products is based on Directive 2001/83 / EC (Two thousand and one Slash Eighty-three slash E C). But the 2012 (two thousand and twelve) version incorporates all the amendments, such as the Pharmacovigilance Directive which defines all concepts, including regulations on the labelling of drug products.

In the 726/2004 / E (seven hundred and twenty-six slash two thousand and four slash E) regulation there is a complementary function introducing various regulations. The consequence is the creation of Community mechanisms and procedures in the area of drug regulation.

In the Directive, the labelling regulations for drug products and boxes are in Title V (five): 'labelling and information leaflets', Articles 54 to 69 (fifty-four to sixty-nine).

- Article 62 (sixty-two) states: "The outer packaging and package leaflet may contain signs or pictograms to clarify some of the information referred to in Article 54 (fifty-four) and Article 59 (1) (fifty nine – one) and other information compatible with the summary of the characteristics of the product, useful to the patient, to the exclusion of any element which may be of a promotional nature".
- Article 54 (fifty-four) concerns the list of information, for instance in bold type: "A special warning, if necessary for the drug".

It is therefore possible to create a centralized pictogram "pregnancy warning". We can therefore have as in France a logo with by the warning mentions.

These regulations support the possibility of creating a centralized danger / pregnancy symbol or pictogram. I count on the EMA to enforce the European patient law. Thank you for your attention.

## ***Karen Keely, FACS Forum, Ireland***

Q1

The risks of taking valproate during pregnancy have been well established over many years. It is clear that valproate carries significantly increased risk of malformations, autism & developmental delay.

We agree with the recommendations from 2014. We accept that treating epilepsy in pregnancy requires finding a balance between the teratogenic risks and the risks of having seizures. Where valproate is necessary, education & doctor-patient communication are key.

As a mother of three adult children, all of whom have been affected by exposure to valproate in the womb, I am living evidence of the risks and the devastating impact of this drug.

Q2

The 2014 measures to reduce risks are appropriate. However, we have concerns about their implementation & effectiveness (we refer to Ireland). The minimum has been done but implementation is often viewed as 'ticking a box', with too little onus on outcomes & delivering change.

SPCs & PILs have been updated with better information. However, not all patients read PILs. On-box warnings (more effective) have only recently been announced and are not yet in circulation. Many patients also receive medications in plastic bags with no box or PIL.

Info materials have been produced by both MAH and the HSE. Neither are fully effective. HSE materials are only found online. MAH materials, while clear and informative, do not use the brand name which is familiar to patients. There are no systems in place to measure effectiveness of materials, which do not appear to be in daily use. Public communications have largely been left to patient groups.

The limited data we have to gauge outcomes shows:

- (1) Doctor-patient communication is increasing but still just 56% report discussing issue
- (2) Valproate use in women is declining overall, but LTIS numbers increasing

Q3

- Ensure that all new and existing measures are outcome-driven and measurable –not activity/task driven.
- Use of valproate resources inc signed checklist should be mandatory for all women of childbearing potential, including those under GP care.
- Establish National registers for women prescribed with Valproate; also registers of children affected
- Establish national implementation groups and include patients/ patient orgs.
- Public awareness campaigns (e.g. use social media) to ensure that ALL women taking drug are aware of risks
- Use brand name(s) on all patient info
- Warnings on external packaging ASAP
- Ensure meds cannot be dispensed without internal & external packaging
- Greater role for pharmacists
- Investigate other aspects of valproate risk e.g. effects on mitochondrial function; effects on third generation, and revise guidelines if needed.

- Activities and campaigns to increase public awareness of reporting ADRs

At this stage, we do not necessarily believe that prescribing guidelines need to be tightened further. However, should outcomes from lesser measures be ineffective after 1 year, this may need to be considered.

## **Clare Pelham, Epilepsy Society, UK**

### **What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?**

There is no doubt that for some women with epilepsy, sodium valproate (SVA) is the only medication that will control their seizures. However the drug is teratogenic and can pose a significant risk to an unborn child if taken during pregnancy, particularly when prescribed at higher doses. Up to 40 per cent of babies born to women prescribed SVA are at risk of developmental issues and about 10 per cent are at risk of a physical disability from birth such as spina bifida.

### **What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?**

Epilepsy Society, Epilepsy Action and Young Epilepsy have worked alongside the Medicines and Healthcare Products Regulation Agency (MHRA) to ensure that women and healthcare professionals (HCPs) have the right information about sodium valproate so that girls and women of childbearing age are aware of the risks associated with the drug. This culminated in the distribution of an MHRA toolkit, launched in February 2016, which included:

- a credit-card-sized patient card to be issued by pharmacists
- booklets for healthcare professionals and patients, with a checklist of key questions and discussion points to be kept with the patient's notes.

Prominent warnings about risks during pregnancy have been added on the labelling of valproate-containing medicines and the MHRA sent a Patient Safety Alert through the NHS Central Alerting System to further highlight risks. They also produced a draft letter for GPs to use to arrange medication reviews for all women and girls in their practice taking sodium valproate.

However, last year when we surveyed more than 2,700 women with epilepsy, 20 per cent of those who were taking SVA were not aware of the harm it could cause to the development and physical health of an unborn child.

This year we have repeated the survey (2,000 women) and found that although this figure has improved slightly, 16 per cent of women taking sodium valproate were still not aware that the drug can negatively affect the development and/or physical health of children born to women taking sodium valproate.

Furthermore, 21 per cent of respondents who were taking SVA had not had a discussion led by their healthcare professional to discuss risks around pregnancy and sodium valproate.

Our survey showed that 86 per cent of women on SVA had seen a healthcare professional in 2017. But more than a quarter of all women prescribed the drug (27 per cent) had not been given information about risks to children exposed in the womb. And almost half, (48 per cent) had not been given information about contraception. Furthermore, 68 per cent of women on SVA had not received the MHRA toolkit released in February 2016.

Although measures currently in place are, arguably, moving in the right direction, the right information is still clearly not reaching the right people. The statistics vary slightly from 2016 to 2017, but the clear and consistent picture is one where approximately 20 per cent or 1 in 5 women with epilepsy who are taking sodium valproate are not aware of the risks or have not been given appropriate information.

The reasons can be many fold:

- there is no NHS audit of women with epilepsy which could automatically highlight those who are taking sodium valproate and flag up the need to call them in for review.
- annual reviews for women with epilepsy are recommended in NICE guidelines but are not mandatory.
- even when digital and print material is made available about the risks associated with SVA during pregnancy, the necessary conversations between patient and healthcare professional are not always happening.
- women with epilepsy often experience memory issues either as part of their condition or as a side effect of their medication. It is vital that warnings are repeated on a regular basis and in written form as well as orally.
- prominent warnings on packaging for medication containing sodium valproate is welcomed but needs face-to-face reinforcement.

### **What other measures should be taken to reduce the risks of using valproate during pregnancy?**

Epilepsy Society is calling on health secretary Jeremy Hunt to make the following change immediately:

**Repeat prescriptions for sodium valproate for women and girls of childbearing age should not be routinely renewed for more than 12 months without a face-to-face consultation with a doctor or nurse. This consultation must include personal and tailored information about the risks around sodium valproate during pregnancy. The information should also be provided in written format.**

This will ensure that women and girls with epilepsy who are prescribed sodium valproate are fully informed about the risks to their unborn baby should they continue to take the drug while pregnant. No additional funding is required for the NHS to make this happen.

We are open to discussing with the NHS how best to make other changes that would result in fewer women unaware of the risks of sodium valproate to their unborn baby. We would suggest for consideration:

- a national audit of all women with epilepsy so as to identify those who are taking sodium valproate and to initiate an annual review
- where a GP is issuing a repeat prescription for sodium valproate, a flagging system should incentivise him/her to take a short e-learning course in order to gain the required knowledge about sodium valproate. This will enable them to appreciate fully the need to discuss risks with all women and girls of childbearing age
- a robust checklist that must be completed before any woman is prescribed sodium valproate. This would record the date that risks around SVA had been discussed and would include a forward plan for follow-up appointments at least yearly. A record would also be kept of all information that had been shared
- Routine checks for women and girls of childbearing age, such as family planning appointments, should also include discussion with relevant women and girls about the risks of sodium valproate during pregnancy; and the provision of written information.

Figure 1. Epilepsy Society website pictogram.



## ***Philip Lee, Epilepsy Action, UK***

Valproate is a very effective epilepsy medicine for some people with epilepsy. However, the drug brings a risk of birth defects and developmental disorders occurring in babies born to mothers taking this medication. Strong clinical evidence of this risk exists and the risk is high when compared to other epilepsy medicines or to women not taking epilepsy medication. MHRA figures suggest that up to four in 10 babies are at risk of developmental disorders if valproate medicine is taken during pregnancy. Approximately one in 10 babies is at risk of physical birth defects. Babies affected by sodium valproate can have severe problems that require lifelong care and support.

Evidence suggests that too many women are still unaware of the risks of taking valproate in pregnancy. This suggests that the measures currently in place are not working. There are no concrete figures to identify how many babies each year are affected by sodium valproate. Data is poorly captured and developmental abnormalities – and their link to valproate - are not always identified until children are older.

A 2016 survey (Epilepsy Action, Epilepsy Society, Young Epilepsy) of 2,700 women with epilepsy showed that almost half (48%) of women did not know that taking valproate in pregnancy could harm their unborn baby. More concerning was that 1 in 5 (20%) women currently taking the drug did not know it can, in a minority of cases, harm the development and physical health of their unborn child should they become pregnant. Epilepsy Action strongly believes the current measures are not enough – women still are not aware of the problems associated with valproate and therefore unborn babies continue to be put at risk of avoidable lifelong difficulties and complications. Epilepsy Action, Epilepsy Society and Young Epilepsy are repeating the 2016 survey and hope to present interim results at the hearing.

Epilepsy Action believes a clinician-led discussion about the risks, ideally before a woman becomes pregnant – pre-conception counselling - is vital to try and avoid risk. This is a recognised intervention currently in place. But the 2016 survey suggests that, despite previous interventions and an incentive, pre-conception counselling is not routinely offered, or at the very least is not implemented consistently.

With the retirement of the QOF indicator for pre-conception counselling, there is currently no formal incentive for clinicians to discuss these issues with relevant patients. We would therefore recommend that discussions with patients that fit the relevant criteria are made mandatory or incentivised through the development of an enhanced service specification. The specification would require all eligible patients to be proactively recalled for a discussion and epilepsy medicine review with their GP. Numbers per practice should be small and therefore this would not be excessively onerous.

***Nathalie Raemdonck, Belgian Association of Victims of Valproate Syndrome (ABVSV/ BVSVS), Belgium***

Bonjour à tous,

**INTRODUCTION**

J'aimerais tout d'abord remercier l'agence de nous accueillir à cette première séance publique. Merci aux associations européennes.

Je me présente aujourd'hui devant vous en tant que maman de deux garçons victimes du syndrome valproate et en tant que présidente de l'association belge des victimes du syndrome valproate afin de représenter toutes les victimes belges.

Je vais vous exposer la situation belge actuelle après que les recommandations européennes aient été décidées

Actuellement en Belgique, les recommandations sont loin d'être d'application :

L'association estime d'ailleurs que ces recommandations devraient être rendues OBLIGATOIRES.

Car on peut constater que,

Le nombre de femmes, en âge de procréer, exposées au valproate restent important même si on constate depuis 2015 une légère diminution.

2014 : les 13-18 ans : 1233 – les 19-49 ans : 13682

2015 : les 13 -18 ans : 1126 – le 19 – 49 ans : 12935 (source AFMPS)

**LE MATERIEL EDUCATIONNEL ET L'INFORMATION AU PUBLIC ET AUX PRESTATAIRES DE SOIN:**

Le matériel éducationnel n'est pas utilisé par les prestataires de soins.

L'information n'est pas systématiquement délivrée à la patiente.

Et au moment, où je vous parle, des enfants en Belgique continuent à naître sous valproate.

En juillet 2016 Une première enquête a été réalisé afin de déterminer l'impact des mesures de minimisation des risques et la communication des risques Cette enquête ne fut pas concluante, de par les moyens de diffusion mis en place, une deuxième enquête plus adaptée est pour l'instant en préparation,

On constate que les campagnes d'informations sont inexistantes, la ministre de la santé en mars 2017 déclarait en commission santé que des campagnes d'informations allaient voir le jour.

Malheureusement à part l'exposition médiatique de l'association aucune campagne n'est prévue.

L'association estime que les médecins doivent pouvoir fournir une information précise sur les médicaments qu'ils prescrivent. Pour cela, Une mise à jour des données doit s'avérer efficace, malheureusement on constate que les canaux de diffusion de l'information ne le sont pas.

Pourtant, en Belgique il existe afin de diffuser une information de manière objective, indépendante et parfaitement documenté, une société qui fonctionne avec des délégués médicaux indépendants en dehors toute contingence commerciale qui propose une mise à jour aux médecins sur notamment les nouveautés les restrictions les recommandations. Cette société s'est vue retiré récemment une partie de ses budgets par décision de la ministre Maggie de Block pendant que des dizaines de milliers d'euros de cadeaux fiscaux sont octroyés aux firmes pharmaceutiques.

Pour toutes les victimes, Il est difficile de comprendre ce genre de décision de la part des autorités.

## **RECENSEMENT DES VICTIMES**

Aujourd'hui en Belgique, il n'existe aucun registre de recensement des victimes du valproate

C'est donc pour cela que l'association estime qu'il est primordial qu'un recensement fédéral puisse être fait et rapporter au niveau européen.

L'association demande notamment que les prestataires de soins soient dans l'obligation de déclarer les victimes;

## **LE PICTOGRAMME EN BELGIQUE**

Quand nous sommes venus en 2014 à l'agence européenne, l'association belge a demandé qu'un pictogramme figure sur les boîtes de médicaments. L'Ema nous a dit que l'apposition d'un pictogramme était une compétence nationale.

Pendant presque deux ans, des nombreuses discussions en commission santé ont eu lieu autour d'une proposition de loi visant à apposer un avertissement visuel sur les boites de médicaments tératogènes;

L'association a participé activement à toutes les étapes des discussions, avec pour objectif qu'un pictogramme avec un text warning puisse figurer sur les boites de médicaments tératogènes.

Malheureusement, la proposition de loi a été rejetée par la majorité parlementaire.

Malgré tout, au regard de la situation française, notre ministre a quand même prit la décision de leur emboiter le pas.

Ce n'est que 8 mois après l'introduction de la demande que nous avons vu enfin arriver sur le marché les premières boîtes de DEPAKINE avec leur pictogramme.

Quant aux laboratoires des génériques, ils n'ont toujours pas introduit de demande, auprès de l'agence.

Pour l'association belge, le pictogramme qui se trouve être primordial, pour notamment un renforcement de l'avertissement aux patientes, doit faire l'objet d'une harmonisation européenne

Comment imaginer que des médicaments à base de molécules tératogènes ne fassent pas l'objet de réglementations européennes qui soient les mêmes dans chaque pays.

L'association considère que l'EMA de par ses compétences doit imposer un consensus européen.

## **LA SITUATION EN HOLLANDE:**

Nous avons régulièrement des contacts avec nos voisins hollandais, les recommandations ne sont que très peu suivies, les patientes commencent seulement à découvrir de quoi souffre leur enfant.

Le nombre de victimes recensées ne fait qu'augmenter. Malheureusement là aussi, si, les patientes sont informées c'est notamment via la presse qui relaye le travail des associations de victimes,

## **EN CONCLUSION**

Les victimes trop nombreuses qui se comptent par 10zaines de milliers, n'auront malheureusement dans beaucoup de cas qu'un avenir toujours dépend de la société.

C'est pour cela qu'il est,

Plus qu'URGENT que les gouvernements, les autorités de santé, les prestataires de soin, l'Europe se mettent autour d'une table pour établir un projet européen cohérent autour des médicaments tératogènes.

Le Softenon, le médiateur, la Dolantine, le dystilbène, le valproate tant de scandales sanitaires qui auraient dû être évité si les autorités compétentes avaient pris conscience de leur responsabilité et des effets désastreux qu'engendre une telle négligence.

Au nom de toutes les victimes européennes, belges, restées pendant des années dans l'ignorance au nom de toutes ces vies brisées, et au nom de mes fils Robin et Jérôme, à jamais plongés dans le monde du handicap confrontés à toutes les difficultés et les épreuves que cela engendre. AGISSEZ ,FINI DE LES SACRIFIER sur l'autel du profit et de l'indifférence.,

### **Translation:**

Good afternoon everyone,

I'd like first of all to thank the agency for welcoming us to this first public hearing. Thank you also to the European associations.

I stand here before you today as the mother of two boys who suffer from valproate syndrome, and also as the President of the Belgian Association of Victims of Valproate Syndrome, here to represent all Belgian victims.

Let me begin by telling you about the situation in Belgium since the European recommendations were passed.

As things currently stand in Belgium, the recommendations are far from being enforced. Our association nevertheless feels that these recommendations should become MANDATORY.

Because, if we look at the current situation, we can see that:

The number of childbearing-age women exposed to valproate is still very high, even if we have seen a slight drop in these numbers since 2015.

If we look at the figures for 2014, we can see that for women aged 19-49 years, 13,682 were still exposed to valproate.

And, turning our attention to 2015, for the same age range of women from 19-49 years, 12,935 women were still exposed.

I'd like now to say something about educational material and information made available to the public and to care providers. Educational material is not currently used by care providers, and information is not systematically issued to patients either. And as things currently stand, children in Belgium continue to be born to women taking valproate.

In July 2016, an initial inquiry was carried out to determine the impact of measures aimed at minimising risks and increasing communication about those risks. This inquiry was not conclusive due to the kind of information-sharing measures implemented. A second, more appropriate inquiry is therefore currently being prepared.

It is clear that awareness campaigns are non-existent. In March 2017, the health minister told the health committee that awareness campaigns would be launched, however unfortunately apart from media coverage of our association, no campaigns are currently planned.

Our association feels that doctors should be able to provide clear and precise information on the medications they prescribe. For this to happen, data need to be effectively updated. Unfortunately, it is clear that information-sharing channels are not being effectively updated.

And yet, in Belgium there is a way to share information objectively, independently and perfectly backed up by documentation: through a society made up of independent medical representatives who are not working for commercial gain. This society suggests providing doctors with updates, in particular regarding new drugs, their restrictions and the recommendations relating to them. This society unfortunately recently lost some of its funding following a budgetary decision taken by minister Maggie de Block, whilst at the same time tens of thousands of Euros were awarded in tax breaks to pharmaceutical companies. It is difficult for any victim to comprehend this kind of decision taken by the authorities.

I'd like now to talk about victim identification.

Currently in Belgium, there is no register which identifies valproate victims. This is why our association feels it is essential that victims be identified nationally and that this list be communicated to the European level.

Our association is calling in particular for care providers to declare the names of victims as a mandatory requirement.

Now let us look at the current status of the pictogram in Belgium.

When we came to the European Agency in 2014, our association asked for a pictogram to feature on boxes of medication. The EMA told us that affixing a pictogram was a decision which fell to national authorities.

Over nearly two years, a number of debates have been held in the health committee about a bill aimed at including a visual warning on teratogenic medication boxes.

Our association has actively participated in every stage of these debates, seeking to ensure that a pictogram with a text warning would appear on teratogenic medication boxes.

Unfortunately, the bill was rejected by parliamentary majority.

In spite of everything, given what has happened in France, our minister appears nevertheless to have decided to follow in their footsteps.

It has taken 8 whole months since the request was submitted to see the arrival of the first boxes of DEPAKINE with a pictogram on the market. And generics laboratories have still not submitted a request to the agency.

Our association deems this pictogram to be essential in order to, particularly, strengthen the warning to patients, and feels that it should be subject to European harmonisation and standardisation. It is hard to imagine why medication containing teratogenic molecules should not be subject to European regulations, which should be identically applied in each member state.

Our association believes that the EMA should use its authority to impose European consensus on this issue.

Turning now to the situation in the Netherlands. We are in regular contact with our Dutch neighbours. The recommendations are barely being followed there either, and patients are only just beginning to find out what their children are suffering from.

The number of identified victims is on the constant rise. Unfortunately, here again patients are only informed because of news coverage about the work of victims associations.

In conclusion, the unacceptably high number of victims, which totals tens of thousands of people, sadly in many cases await nothing more than a future where they are dependent on society.

That is why it is more URGENT than ever that governments, health authorities, care providers and Europe come together to draw up a coherent European plan for teratogenic medications.

Softenon, Mediator, Dolantine, Dystilbene, valproate has caused so many health scandals now that could and should have been prevented, if only the competent authorities had accepted their responsibilities and the disastrous effects provoked by such negligence.

On behalf of all the European and Belgian victims who have been kept in the dark for all these years, on behalf of all those shattered lives, and on behalf of my own children Robin and Jerome, forever sentenced to their disability and faced with all the challenges and difficulties that this entails, please, LET'S ACT NOW! LET'S STOP SACRIFICING THEM in favour of profit, and in favour of indifference.

## ***Martin Brodie, International Bureau for Epilepsy (IBE)***

### Question 1

The International Bureau for Epilepsy (IBE), the organisation we represent here, was established in 1961. It is an international network that now encompasses more than 135 national epilepsy organisations (IBE chapters) worldwide. It exists to provide support for our global network and to facilitate the development of new chapters in underserved areas of the world. We encourage communication and collaboration among all members in order to meet our global mission and vision. Our members are patient/family focused and driven organisations and we work collaboratively with our professional and government partners worldwide. In view of this, our position with respect to the use of sodium valproate (VPA) seeks to ensure that public information and that health education are safeguarded, while advancing advocacy and international best practice exchange.

VPA was licensed for the treatment of epilepsy in 1967 and is also widely used for bipolar disorder and migraine. It is widely regarded as the drug of choice for the idiopathic generalized epilepsies and is also frequently prescribed for focal epilepsies with or without secondary generalization. VPA has been recognised as teratogen for many years, as have other antiepileptic drugs, such as phenobarbital and topiramate. Like all these agents, the teratogenicity of VPA is known to be dose dependent with a substantially reduced risk at doses of 500-700 mg daily, which can be therapeutic in some patients with newly diagnosed epilepsy. There is also the potential of using low dose VPA with lamotrigine, which is the only proven synergistic combination of antiepileptic drugs.

Uncontrolled epilepsy, particularly in young people, carries a risk of sudden unexpected death (SUDEP) and so leaving seizures, especially tonic-clonic seizures, uncontrolled is not an acceptable option. I have patients, particularly those with idiopathic generalized epilepsy, for whom VPA proved to be the only successful treatment. We accept the need to restrict its use in young women, but would support its prescription as a drug of last choice, if all other approaches prove unsuccessful. In addition, there are many women who do not have pregnancy in their life plan. Both these categories of patient should have the option of taking VPA after careful, accurate and sensitive explanation of the risk-benefit ratio to all concerned. VPA is an effective and well tested antiepileptic drug that should not be discarded as a therapeutic choice for every young woman with epilepsy.

### Question 2

There has been no consistency in presenting the risk-benefit ratio of VPA use for suitable patients, particularly those with idiopathic generalized epilepsy for whom drug choices are more limited.

### Question 3

IBE believes in public information, health education, advancing advocacy and international best practice exchange. Thus, a well organised and professional education campaign should be set up in all EU languages. This could consist of properly

## ***Josephine Tapper, Patient, member of Bipolar UK***

### **Introduction:**

Firstly I would like to thank the EMA for allowing me to speak at such an important Hearing. Although my title states that I am a member of Bi-Polar UK, I stand here as an individual woman with Bi-Polar who has received no input, or indeed support from any mental health organisation. My thoughts are mine, and mine alone and aren't evidential.

### **Question 1: What is your view of the risks of taking Valproate during pregnancy, including its potential effect on the child?**

As a woman bi-polar I battle with feelings of inadequacy, shame and guilt. Therefore I was petrified of getting pregnant whilst taking Valproate due to its proven toxicity. All medical data has, for a number of years clearly shown a direct correlation between the drug and foetal abnormalities, and/or developmental problems in the child once born. Women with bi-polar on Valproate may well be on other medications to treat the same condition, or co-morbid illnesses, potentially complicating pregnancy further. They are also at far greater risk of depressive episodes during pregnancy, postnatal depression and/or postpartum psychosis. Any birth defects that arise due to Valproate use also increase pressures on the long term mental health of a mother with bi-polar.

### **Question 2: What are your views on the measures currently in place to reduce the risks of using Valproate during pregnancy?**

For a number of years UK guidelines have stated that Valproate should not be prescribed for women of childbearing age. I have always had a very strong desire to have children and continually expressed this to my mental health teams. However for a number of years I had an unsympathetic psychiatrist who refused to stop prescribing Valproate, despite my concerns and requests. I was actually told 'perhaps given your illness you shouldn't have children', although I had never, and indeed have never been detained under any Mental Health Act. Eventually my medication changed, but only after I was placed under the care of a different clinician. In the last few years I have had psychiatrists who have been more supportive, but they are poorly equipped in discussing issues around pregnancy and bi-polar. I am now on a mood stabiliser that carries far fewer risks to the unborn child than valproate. However, this is too little and too late for me. At the age of 46 I know that the opportunity to carry my own child has passed and I will have to live with a profound sense of sadness and regret for the rest of my life. These feelings have a negative impact on my mental wellbeing and recovery and I will always grieve. I hope that psychiatrists no longer adopt the same prejudiced and unsupportive approach that mine did. However, I suspect there are still pockets of bad practice.

### **Question 3: What other measures should be taken to reduce the risks of using Valproate during pregnancy?**

At no point was I ever been given any information, written or oral on the risks of Valproate in pregnancy. I was a relatively engaged patient but was only told about the risks by another service user not by psychiatric services. All patients on Valproate who are considering pregnancy should be offered counselling on its pharmacological dangers. Guidance must be clear, evidence-based, and free of bias. There should also be sign posting to other agencies where necessary. Clinical and social support at this stage is critical so that a woman's mental health is not jeopardised by any sudden changes to, or withdrawal of medication. A woman who feels included and involved in her care plan is more likely to comply with treatment resulting in a more positive experience of pregnancy and better health outcomes for her and her child.

However, many women will discover they are pregnant whilst taking Valproate. Given the current pressures on Mental Health services it is likely to be a General Practitioner who will be the initial point of contact for these women. There should be an immediate referral to the relevant mental health services without the usual waiting time, even where a woman may have previously been discharged. Valproate titration can then begin and other drugs and/or therapies introduced where necessary. There should also be joint input from General Practitioners and hospital and community maternity services to create a multi-disciplinary care plan focussing on the physical and psychological.

Finally psychiatrists entering the profession today should be better trained in the area of pregnancy and bi-polar. The same could also be said of obstetrics and midwifery. Women with bi-polar have multiple health burdens and may have additional support needs. However, they are no different to any other group in their ability to provide loving, stable and positive family environments. The stigmatising attitudes of the past should have no place in psychiatry and the medical profession as a whole today. It is my fervent hope that women with bi-polar considering pregnancy be supported in a way that I wasn't. They should be respected and enabled to make an informed decision based on their individual circumstances and aims; perhaps the most important decision they will ever make in their life.

## **Joanne Cozens, Organisation for Anti-Convulsant Syndromes (OACS), UK**

### Question 1

#### **What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?**

OACS Charity received responses from families affected by Fetal Anti-Convulsant Syndrome (FACS).

We created a questionnaire and shared it across families with Children affected by FACS.

We asked members what Health Care Professionals (H.C.P) informed women of the risks of taking Valproate before pregnancy.

- What they knew prior to pregnancy
- What they did to keep their baby healthy

In responses:

- Most responders mentioned a statistic of 1-2% chance of child being born with spina bifida and cleft palate.
- There was no mention of neurodevelopmental delays, Autistic Spectrum Disorders and Low I.Q.
- Many women were told to take folic acid

Evidence:

- Our survey shows that most of our women given Valproate, were under the impression that it imposed insignificant risk to the unborn child
- 90% of respondents asked their H.C.P whether it was safe to take Valproate during their pregnancy.
- Other H.C. P's didn't mention the dangers it may cause to the foetus.
- OACS surveyed members about their preparation to start a family. Women advised that they had a healthy lifestyle to ensure a healthy pregnancy, by cutting out alcohol, smoking and improving diet.
- Followed by advice from their H.C.P's, most took a higher dose of folic acid.

Women followed the general advice from H.C. P's.

- The evidence shows that our members accepted that the risks were negligible (1-2%).
- The parents were prepared to do whatever they could to prevent harm to their children.
- It is extremely clear from the survey, that these women would never take a risk involving a 10% chance that their child will be born with major or minor congenital malformations and 40% risk of Neurodevelopmental delays

Statements of the families affected by Valproate

*"To be honest, disgusted, these children and families have been let down not just by Sanofi but by the government, by the system, by the NHS, fighting for basic care, disability benefits, chasing professionals, it's pretty disgraceful, we as a family have been put through hell, called liars told we are fabricating our daughters condition, which is absolutely ridiculous, the ignorance and lack of education*

*surrounding this catastrophic, debilitating rare disease is as bad as the disease itself, knowing this man made condition could have been stopped is heart-breaking"*

*"I worry about the future, I worry about what will happen to my gorgeous little girl, when I'm gone, we feel hopeless."*

*"As a family, we don't go on holidays together"*

*"My Son keeps asking questions that I cannot answer regarding his future"*

*"I have lost our house due to the cost of caring for a child with FACS, we had a mortgage before all of this started but increasing medical expenses, there was no way out"*

*"My career has been impacted due to the time that I needed to take off work, for many hospital appointments and operations"*

*"As a family, we lose out on family gatherings, with friends and family because my Son's continuous meltdowns"*

*"Watching your child grow up with no friends at the age of 17 is heart breaking"*

*"Your child not being able to learn to drive like any other 17 yr olds"*

*"Watching your child being bullied at every level of school and not having an answer"*

*"Knowing that you may never become a grandparent"*

*"Knowing that your Child will never have total independence, living on their own or with their own family"*

*"Worst of all the feeling of watching other children giving hugs and cuddles to their Mums, knowing it will never be like that for me"*

*"Even the simplest thing of having an engaging two-way conversation never happens in our family life"*

*"It's hard to imagine what normal life would be like, it's been like this for 17 years now. Whenever you think that you have things under control, something else happens to our child's health and wellbeing because of FACS"*

*"We long for our child to experience life, like other children"*

*"All any parent desires are that their Child grows up into a fine young man or young lady, set up to go out in the big wide world."*

*"Watching my child laying in a cot bed at the age of 19, whilst my other children go off to hospital appointments with their own chronic health conditions caused by Valproate"*

*"Attending to all my child's personal things like washing her down 3 times a day, putting nappies on her, feeding her most of the time by mashing up her food so that she doesn't choke, dressing her and changing bibs to catch her saliva is just part of her daily routine"*

*"The pain of watching my child having 7 or more different types of uncontrolled seizures, 20 – 30 times a day"*

*"Waking up in the morning looking at my child wondering if this will be the last time I see her smile, she has a do not resuscitate letter when her health deteriorates"*

*"The pain of having a picture of your child's coffin on your phone, so that it prepares me for the day that she loses her fight from the effects of Valproate"*

*"I am mourning my child now and will be mourning the death of her when she's gone, this is the result of Valproate, no parent wants to see their child slowly die in front of them"*

*"Let's face it, the whole families lives are taken up by complex chronic health problems"*

*"The horror and shock I felt when I realised that the Epilim I took whilst I was pregnant was also called Sodium Valproate"*

*"I will never forget what my genetics doctor said, the realisation that it harmed my boys will haunt me until I die"*

*"It is very easy to go down the route of having a therapeutic abortion, when you are told that your child has spina bifida & fluid on the brain (hydrocephalus) with little expectation of quality of life, Brain Damage!"*

*"I held three babies and watched them die, no one wants to address this"*

## **Question 2**

### **What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?**

OACS Charity is concerned about how this information is delivered inconsistently throughout all H.C.P's

- All departments of health within the devolved Governments in the UK have completely different systems within their health authorities
- Many of the Clinical Commissioning Groups (CCG's) got the information over a year ago, regarding the updated information on the risks of Valproate, directly from the MHRA
- CCG's have done the bare minimum feeding the information by email to the H.C.P
- H.C.P often open emails but have stated that they are too busy to read them and get email fatigue
- Only now the toolkit is being received, since the announcement of the EMA review H.C.P's and Pharmacies are only now receiving their booklets and cards
- H.C. P's are having difficulty with responding to the warnings and the toolkit because they haven't received the relevant training or information to enable them to carry out a very sensitive job
- It's a postcode lottery whether the information is fed down from the H.C.P to their patients
- More action is needed with a clear collaborative approach across the whole of Europe
- There is no sharing of information or strategy in place to enable the H.C.P's to act

The proactive action of Kim Morley, who created a course for Midwives informing them of the updated information on Sodium Valproate and the risks associated with pregnancy. This initiative was well received and midwives claimed CPD's to enhance their continued learning and career path.

## **Question 3**

### **What other measures should be taken to reduce the risks of using valproate during pregnancy?**

OACS Charity have been told that using a Centres for Medical Services (CMS) alerting system, which is the web-based cascading system for issuing alerts and important public messages and other critical information safety guidance. OACS Charity feel that if something like this was used in Europe, safety messages such as that of Sodium Valproate and pregnancy will get out quickly and easily.

It has been suggested by pharmacists that there needs to be a clear symbol on the box to ensure that the pharmacist is able to quickly identify a drug that should not be given to a pregnant woman. Following an initiative from France, all European countries should deliver a consistent message to women of child bearing age. APESAC have designed a silhouette of a pregnant woman in a no entry symbol, we feel is just right to deliver a message not just to pharmacists and H.C. P's but to their patients.

OACS Charity have looked at the traffic light prescribing system, and have found that it is still prescribed for Epilepsy as a Green Light drug and for Bi-polar as Amber Light. We believe that Sodium Valproate should be a Red-Light medicine, that is only given by professionals who understand the risks of this medicine. This has become so much more important, as there are moves to use this as an off-label drug.

An advertising campaign should be directed to ensure that all patients are found, so that the correct information is given along with informed choice, this can quickly be carried out by putting the warnings on exiting waiting room advertising display screens, in all areas with little or no extra cost, combined with patient group literature informing of support groups for families affected by Valproate.

Patient organisations who are experienced and understand the challenges faced by those who have taken sodium valproate during pregnancy, should be included in the contact details on the toolkit. No one knows the effects of sodium valproate, as person who lives it and their families and carers that watch over them

Mothers have been affected by adverse drug reactions including complex, chronic health problems, all are known side effects of sodium valproate listed in the Patient Information Leaflets (PIL). Women need to be properly tested for the toxic effects of sodium valproate, to ensure that their safety is a priority with no lingering side effects. Europe has clearly not learnt the lessons of the Thalidomide Tragedy.

Valproate is a medicine known to enhance oxidative stress and cause secondary mitochondrial dysfunction; Valproate is known to aggravate chromosomal and some genetic disorders creating complex and life threatening medical conditions. There needs to be a more robust approach to test for severe and secondary mitochondrial disorders.

It is time to make core changes into the way medicine is tested for teratogenic properties. OACS understands that sodium valproate is needed in a small group of people, so it's time to review the safety protocol for it.

#### **Testing for the vulnerable groups:**

- To include those with genes such as POLG, and some chromosome disorders, where by sodium valproate is known mutate the genes
- Depending on potency, if a drug has a mitochondrial liability, it will have toxic repercussions
- Many papers suggest looking out for low carnitine and high lactate levels
- To test to ensure that depleted vitamins and minerals are replaced
- Sodium Valproate, is an inexpensive drug, but its effects cost the European Health System Billions due to its adverse effects

#### **Treatment of manifestations:**

- Clinical management of Sodium Valproate largely supportive and involves conventional approaches for associated complications including physiotherapy, speech therapy, nutritional interventions, respiratory support, and management of seizures and movement disorders. Depending on potency.
- There needs to be a re-think on how H.C. P's manage the toxicity of Valproate giving women the correct information and advice regarding the affects, that toxic medication has on the entire body, cognitive effects and mental health problems.

## **Emma Friedmann, FACSWARE.NET, UK**

#FACSAware is an online awareness campaign. Statement written by Emma Friedmann.

### **Overview 2015-2017**

The MHRA Valproate Toolkit is an excellent example of co-production and stakeholder engagement.

All suggestions made in 2014, page 7 of FACSAware report for PRAC have now been completed.

The dissemination has been inadequate due to the UK Government imposed restructure of the NHS and the fragmentation the reorganisation and increased privatisation has caused.

Although it makes economic & ethical sense to reduce risk, it is clear that UK Patient Safety is not currently a priority for Department of Health, NHS England & NICE.

### **Further work**

#FACSAware supports the banning of this product for use in pregnancy as the benefits do not outweigh risk and pregnancy is not mandatory. Babies exposed have a high probability of lifelong disability causing physical and emotional harm & suffering.

It would be beneficial to have a symbol of a pregnant woman in a red circle and strike through on the outside of the boxes.

This has been discussed at the Valproate Stakeholder Network meetings but not followed through due to concerns by a professional that women might become confused and think it is a contraceptive or day after pill.

### **Challenges**

#### **Primary care**

NHS Drs are short staffed & are not reading MHRA Drug Safety Updates & NICE Guidelines.

Some GP surgeries have fortnightly meetings to discuss safety and clinical updates, this is good practice but it is not happening everywhere.

The challenges facing General Practice have led to Dr Vautrey, Chair of the GP Committee at the BMA to express concerns about GP list closures, Retention & Recruitment issues and Patient Safety.

Janet Davies, General Secretary of the Royal College of Nurses has expressed concern over short staffing and fears regarding patient safety.

This short fall in staffing is part due to the Department of Health policy changes on the NHS and it's structure. Drs do not prioritise reading safety data & this problem is made worse by the increasing use of locums and agency staff.

#### **NHS Trust Management**

Many NHS Trust CEOs have not forwarded the Dear Dr letter to professionals in contact with patients taking Valproate.

#### **Pharmacy**

The cards to be given to the patient when they collect their Valproate prescription from the pharmacy have not been sent to the majority of pharmacies visited.

The letter accompanying the cards did not have the MHRA logo on it & did not look official.

## **NICE**

When a Dr is aware of the Valproate Toolkit they have nowhere official to look for information on the syndrome & the clinical pathways recommended for use. NICE have no information about valproate syndrome on their website and the Valproate Toolkit isn't on the first search screen.

Patients need to have a discussion with their Dr, without information the decisions cannot be informed.

Drs who need to transfer a patient from VPA to another AED have no guidance from NICE on the process, so they have to refer the patient to Neurology services who have a 6 month waiting list.

## **Department of Health**

Roundtable meetings have been held at the Department. Unaware of any actions taken as the MHRA have been managing and coordinating this project in line with statements by Ministers that this is a regulatory issue and nothing to do with them.

## **Charities**

Major charities have not promoted risk as much as they could have and their outdated & misleading leaflets are still in NHS waiting rooms.

## **Declaration of Interest**

There are people who take part in the MHRA Valproate Stakeholder Network meetings who have been paid directly or indirectly by Sanofi. They have never claimed to be speaking on behalf of Sanofi but they have not made clear their connections past or present.

## **European Union member states**

The absence of statements by EU patient groups shows there is a lack of awareness in the majority of the EU.

## **MHRA AND EMA**

Both regulators have been brilliant and the achievements should be celebrated.

We are hopeful that the action taken on Valproate will help in the development of a blue print for future regulatory warnings.

***Branwen Mann, Patient representing Anti-Convulsant Syndrome, OACS Youth Trustee***

I am an individual with Fetal Valproate Syndrome, I am here today to speak for those who have been exposed to valproate in the womb.

I know that the full harm done by sodium valproate is barely understood or even recognised by anyone other than the family that live it. The effects have been so intense, that many of us struggle to lead a 'normal' life. Every day we struggle with life limiting, complex and rare health problems. Symptoms change, develop and new ones come in. The oldest child I have spoken with is 46 and in a home for dementia.

I love the toolkit but I do not understand why the patient led support groups for fetal anti-convulsant syndromes who have experienced and understand the challenges faced by those who have taken by sodium valproate during pregnancy not included in the contact details on the toolkit? No one knows the effects of sodium valproate as the people who live it. Please add us today.

Why? if you are seeking out women who took sodium valproate, why, can you not seek out the lost children of valproate. These children; whatever their age, and their families need to be found, they need help – please.

Sodium valproate is no longer given to women of child bearing potential, except of course when truly needed. Women are now being given an informed choice, that empowers them to take the next step forward with their lives, with a healthier and clearer frame of mind. I truly believe that in the future Fetal Valproate Syndrome will be an ultra-rare disease in the future. Please make this happen today.

Sodium Valproate has not just affected the children. I have watched my mum. The adverse drug reactions of the medicine; the oxidative effects have caused many chronic health problems for her, as it has for many of her friends from OACS Charity. There needs to be a National Patient Safety Agency Book for Sodium Valproate. This would be given to ALL patients who take Sodium Valproate. This is a mitochondria toxic medication; patient safety should always come first, be responsible.

Like many others my mother is a victim of irresponsible prescribing. This is a practice that has to stop now, patient safety, and responsibility.

The Committee of Safety of Drugs began the yellow card alert system in response to thalidomide, the committee of safety of medicines provided the framework, the Medicine and Health Product Regulatory Agency is responsible today. It is the poor promotion of this valuable tool that brought us here today. Reporting Adverse Drug Reactions should be an educational necessity for our personal wellbeing. It most certainly should be taught in level one for anyone working within the health care professional. This is good economics can you address this?

I was recently told that I could die at any time, I want to make use of my life. I stand here as a representative of harm done. should never be used again. I am going to walk away from here trusting that you will make the right choices.

***Christine Smillie, Patient representing Epilepsy, UK***

Q/1

Unfortunately I am well aware of the risks of taking this drug. At the age of 33 I had my first episode with Epilepsy. I was prescribed Epilim, and continued with life. My first child is thankfully healthy, but before I had my second child my dosage was increased and it was during this pregnancy whilst having scans that concerns started. My son arrived a month early and it was only during the next few months we even became aware of Fetal Aniti Convulsant Syndrome. Upon meeting with the most helpful paediatrician who felt my son was behind in his development and concerned that his appearance might suggest some underlying problems. He arranged for us to meet with a Geneticist who confirmed "Delayed Development-Effects of Epilim During Pregnancy". At least during these early years he had full support for all of his many needs. As they get older this disappears, schools are not interested. He is now Moderate to Severe Delay in Development due to Epilim F.A.C.S as I know it. But no one knows what this means, you cannot put that on a C.V. He has no support and does not fall into any category for help. It is not a recognized condition.

Q/2

There is still not enough information/advertising about this drug and its effects on the children. People have had their lives changed as they struggle to bring up the Valporate children. Until people in the street know what FACS is the job is not done. My son is now 19 and we still have to explain to DOCTORS what his problem is.

Q/3

Again there is not enough advertising about the consequences of taking this drug. The problem has been with us for decades. Surely we are at the stage where it should be banned or not prescribed to women of child-bearing age at all. (unless completely necessary with dangers outlined, if we still have to tell doctors about it, how are they spreading the word?)

As I from a personal point of view feel that no-one is prepared to take the responsibility of the damage that this drug causes.

## **Samantha Ashby, SUDEP Action, UK**

The risk to children of women with epilepsy (WWE) who take Sodium Valproate is well documented. Measures are in place to ensure clinicians, their patients & families receive information about the risk to children linked to medication. As with many aspects of epilepsy care, more can be done to ensure this information is given in a standardised way. However, we know first-hand from the work SUDEP Action has undertaken for 21 years as the only UK charity dedicated to raising awareness of epilepsy risks & supporting those bereaved by epilepsy, that when it comes to epilepsy risk discussions, standardized messages even if there are resources, doesn't always happen.

This hearing focuses on the risk of valproate use during pregnancy & the reduction of risk. But vitally these messages must be balanced: focusing not only on the risk to child, but giving equal weight to the need for mum to understand the risks to herself too. Today's media promotes 'bad news' stories about those affected, scaremongering WWE who read them – meaning rash decisions could be made in lieu of information about the importance of how keeping herself safe is just as vital to her baby as making sure her AED doesn't harm. But often this message struggles to be significant aspect to this topic.

WWE must be told about the importance of continuing their AED until directed otherwise, & the potential consequences of not doing so; increased seizures, injuries, death. 1:1000 WWE die during or shortly after pregnancy (Nashef, 2014). There are approx. 1200 epilepsy deaths annually in the UK (1/2 are Sudden Unexpected Death in Epilepsy; SUDEP), and 42% of epilepsy deaths are potentially avoidable (Hanna, 2002). The condition kills more year than Asthma, another Long-term Condition, but one with a population 9x larger. The Centre for Child & maternal Death Enquiries flagged in 2012 how WWE didn't receive risk information & that clinical understanding of risk was low. Many of the women (who died from their epilepsy) stopped their AEDs fearing it would harm their child.

Current Valproate literature discussed this issue; but not specifically enough. We know as few as 4% of clinicians discuss epilepsy risks & the potential of death (Waddell, 2013). So it is unlikely that without a strong steer, clinicians may not stress this importance & WWE many not realise the dangerous consequences if they stop their medication. This cannot be shied away from & must be central to epilepsy risk discussions to help reassure & educate women; allowing them to make informed choices about their care. And hopefully reducing the number of maternal epilepsy deaths each year; But this can only happen if Valproate risk discussions are balanced.

"Only one week prior to S's death she received a letter from her clinician telling her that she was a very low risk patient & didn't need to take her AEDs. S wasn't aware of the risks" (S was a student nurse who was 7 months pregnant when she died of SUDEP, aged 25)

### ***Sam Gray, Patient representing Epilepsy, Ireland***

I was diagnosed with Epilepsy and prescribed sodium valproate at the age of 16 (2010). Since then I have entered medical school and in 12 months' time will be a qualified doctor. My experience with Neurology at that formative age has made me passionate about Neuroscience and last year (2016) I took a year out of med school to earn an MSc in Neuroscience. I would like to speak on my experience of the medication, clinically and academically but more importantly as a patient, including a reduced attention span and sporadic difficulty concentrating which I have discussed with my Neurologist over the years, and including the time I briefly changed to Clobazam before coming back to Sodium Valproate. I consider my experience on sodium valproate a positive one but wish to draw attention to these cognitive effects I have noticed.

# Pharmaceutical companies

## ***Eric Teo, Sanofi***

Sanofi's summary to Pharmacovigilance Risk Assessment Committee (PRAC)

Sanofi has actively contributed to the previous and current PRAC European reviews on the use of valproate during pregnancy.

Sanofi would like to provide its view on the 3 questions raised by the PRAC for this Public Hearing considering the benefit-risk profile of this essential medicine.

Question 1; risks of using valproate during pregnancy

When considering the risk of using valproate during pregnancy, one should balance the risks associated with epilepsy including sudden unexpected death in epilepsy (SUDEP), versus the benefits and risks associated with the treatments including valproate. Valproate is regarded as the most efficacious treatment for certain forms of epilepsy, while the risks include malformation and below-average developmental ability in children exposed in utero.

Question 2; effectiveness of risk minimization measures

In cooperation with the European and National Authorities, Marketing Authorization Holders, including Sanofi, have implemented a number of risk minimization measures. The latest interim analysis of the Drug Utilization Study which looked at the effectiveness of the risk minimization measures showed that the pattern of use of valproate in women of child-bearing age had not changed significantly. However, this analysis also showed that the number of pregnancies in women using valproate had fallen by more than half.

Question 3; additional measures

Sanofi's proposal for discussion with the PRAC includes enhancement of the existing risk minimization measures, in particular, revised educational materials and consent form, medical consensus guidance on the use of anti-epileptics before and during pregnancy, pregnancy tests for specific groups, and "pop-up" electronic reminders embedded in prescribing and dispensing software.

In conclusion, valproate is an important treatment that many women continue to rely on to control their disease. All stakeholders have key roles in optimizing the effectiveness of the risk minimization measures.

# Healthcare professionals and academia

## *Jurate Svarcaite, Pharmaceutical Group of the European Union (PGEU)*

1. Every effort should be taken to reduce the risk of exposure of valproate to females of child-bearing potential. Lessons learnt from thalidomide and retinoids should be heeded - RMMs should not prevent an effective treatment for a suitable patient, but regulators and manufacturers must engage more effectively with stakeholders (HCPs and patients) to ensure the RMMs actually work in practice.

2. Patients often forget their card, paper materials are lost in dispensaries, communications from manufacturers are sometimes disregarded as unwanted marketing. These well-intentioned RMMs should be systematically distributed and implemented in practice, but currently they are not. Pharmacists need to be consulted earlier on in the development of standard and aRMMs to ensure the RMMs are fit for practice and can be easily implemented.

3. - Materials (e.g. patient card) could be placed on the outside of medication packaging in order to trigger dialogue between pharmacist and patient at point of dispensing

- RMMs could be systematically described in academic publications, scientific or professional conferences / publications

- RMMs could be selected for inclusion, or form part of continuing education (CE) or continuous professional development (CPD)

- Greater use of multiple media channels to disseminate RMMs, ensuring user-tested, plain language and appropriate graphical representations are used

PGEU would like to highlight some best practice examples from PGEU members to raise awareness and reduce the risks of using valproate:

- Electronic decision support messages within pharmacy software concerning risk minimization and contraindications

- Articles or communications in professional journals / publications (eg. in France in 'Le journal d'Ordre national des pharmaciens' and Ireland in the 'Irish Pharmacy Union Review Clinical Tips') which explain the RMMs, how they should be used and how to engage with patients

- Promotion of CE / CPD courses for pharmacovigilance, risk minimisation and on specific medicines such as valproate (eg. in the UK with CPD articles like 'Concerns with using sodium valproate to treat epilepsy in pregnant women' from the Royal Pharmaceutical Society)

- Newsletters or articles on professional associations' websites providing updates, summaries and further links to risk minimisation measures or updated product literature (eg. in France 'Valproate et dérivés : nouveau pictogramme sur les conditionnements' from the Ordre national des pharmaciens and in Germany 'Valproinsäure/Valproate: Umsetzung des Beschlusses der Europäischen Kommission zu Änderungen der Produktinformationen' from the Bundesvereinigung Deutscher Apothekerverbände)

- Publication of 'Quick Reference Guides' (or similar) on valproate such as 'Dispensing valproate for girls and women' (Royal Pharmaceutical Society, UK)

- Additionally, PGEU recently introduced a dedicated chapter for our twice-monthly member newsletter dedicated to all EMA and pharmacovigilance news

***Helen Cross, European Reference Network for Epilepsy (EpiCARE)***

We recognise and acknowledge that use of valproate during pregnancy poses a significant risk of harm to the unborn child. However, sodium valproate remains an extremely useful antiepileptic medication, of considerable benefit in some of the rare and complex epilepsies. Although we acknowledge that this hearing is to address actions put in place to minimise the risks of valproate in women who are pregnant or of childbearing age, our concern is that such measures may hinder use in individuals with these rare epilepsies and therefore compromise seizure control and quality of life. Many of these individuals have severe learning disability, and risk benefit of use of the medication needs to be considered. We ask that use in individuals with rare epilepsies such as Dravet syndrome and others may require different consideration, particularly as approaching child bearing age, as use of the medication may offer greater benefit than risk.

***Timothy Barrett, University of Birmingham, UK***

I am Chief Investigator of an international clinical trial of sodium valproate in a rare disease, Wolfram syndrome. I previously sought EMA Protocol Assistance (EMA/H/SA/3087/1/2015/PA/II and EMA/H/SA/3087/1/FU/1/2017/PA/II) on the design of the safety aspects and efficacy measures for the trial. Wolfram syndrome is a rare, devastating, life limiting disease for which there is no cure and no treatment. I would like to make the following points:

- a) Sodium valproate can be investigated for new indications
- b) We have evidence that valproate can slow down the disease process and improve quality of life in Wolfram syndrome. We will investigate this in a clinical trial following the safety recommendations of the national and international regulatory agencies.
- c) To answer the questions: we recognise that sodium valproate treatment during pregnancy poses a risk to the unborn child; the current measures will minimise the risk of valproate being used during pregnancy; other measures should include increased dissemination to healthcare professionals and members of the public, to raise awareness of the dangers.
- d) While we recognise that the use of sodium valproate should be carefully regulated, it is important that it should remain possible to investigate new uses for the medicine, particularly in life threatening conditions where there is no current treatment.

***Daniel Hawcutt, Royal College of Paediatrics and Child Health (RCPCH), UK***

Question 1 (risks of taking valproate during pregnancy): Acknowledge the risks to the child from valproate in pregnancy are significant. Compare with other anti-epileptics (lack of evidence versus lack of harm)

Question 2 (views on current measures to reduce the risks): Highlight that children have not been considered as a separate population with their own diseases (which may remit before puberty), in which valproate has established efficacy. Also highlight the additional UK material on risks of valproate in pregnancy designed with, and specifically for, children and young people.

Question 3 (other measures should be taken): This is the main area we wish to comment on, where we wish to provide information on how paediatric epilepsy differs from adults and therefore how any consideration of additional measures should be done in an age specific way, to ensure treatments that have evidence of efficacy in children are not inadvertently lost as an extension of developing good practice aimed at adult populations.

## **Torbjörn Tomson, International League Against Epilepsy (ILAE) (CEA)**

### Question 1

What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?

Response: We believe there is strong evidence that the risk, compared with no use or use of many other antiepileptic drugs, is increased for major congenital malformations, impaired neurodevelopment and probably also for adverse behavioural development, and that this increase, at least for congenital malformations and most likely also for impaired postnatal cognitive development, is dose dependent.

### Question 2

What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?

We agree that valproate, whenever possible, should be avoided in girls and women that might become pregnant while on treatment with valproate.

However, epilepsy is a serious condition and uncontrolled seizures may have devastating consequences (including death), and for some patients valproate is the most and sometimes only effective treatment. It is important that the restrictions do not force those in need of valproate to continue to have uncontrolled seizures on a number of other medications before they can be prescribed valproate, particularly when the risk of becoming pregnant while on treatment is minimized. The restrictions should therefore make exception, and permit first line use of valproate, when it is the most appropriate drug for the patients' type of epilepsy, for girls and women where future pregnancies are extremely unlikely due to e.g. other concurrent disabling conditions and/or very severe epilepsy. Hence, the restrictions should apply for those of childbearing potential not for other girls and women.

The restrictions should also make a distinction between girls and women that are of childbearing potential and those that are already pregnant. As formulated presently, the restrictions may be interpreted to suggest withdrawal of valproate also during pregnancy with significant risks regarding loss of seizure control in a critical period and without any data indicating reduced teratogenic risks.

### Question 3

What other measures should be taken to reduce the risks of using valproate during pregnancy?

Neurologists are probably better informed than other categories of prescribers. Hence it is important to reach out to other potential prescribers, e.g. psychiatrists and general practitioners.

Information should also include reference to the dose-dependency of the teratogenic risks prompting prescribers to use the lowest effective dose when valproate is considered necessary

## ***Anthony Marson, European Academy of Neurology (EAN)***

I am an academic neurologist (epileptologist) with extensive experience in the management of epilepsy and in assessment of the benefits and harms of antiepileptic drugs.

I led the SANAD trial which provides the best evidence about the clinical and cost effectiveness of valproate when used as a treatment for generalised or unclassified epilepsy. I am also the coordinating editor of the Cochrane Epilepsy group and have lead two major systematic reviews that have assessed developmental outcomes and malformation rates following in utero exposure to antiepileptic drugs.

Treatment decisions in epilepsy require an assessment of benefit and risk and their trade offs, which need to be communicated to women in order to allow informed treatment decisions.

We must remember that uncontrolled epilepsy is associated with death, injury and other co-morbidities.

### Question 1

What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?

Wherever possible valproate must be avoided in pregnancy.

There is no reason to prescribe valproate to women with focal epilepsy who are of child bearing potential.

For women with idiopathic generalised epilepsy (particularly JME) valproate is the most effective treatment. When starting treatment (for women who are not pregnant or planning pregnancy) the pros and cons of valproate and alternatives should be discussed to inform a treatment decision. In my view it is unethical to withhold the most effective treatment from women should they wish it to be prescribed. Experience is that most choose an alternative.

### Question 2

What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?

For epilepsy, current alerts and messages to epilepsy specialists are adequate.

The main concern is the prevalent population not in specialist care. More definitive action must be undertaken to identify these individuals in order to plan future care.

### Question 3

What other measures should be taken to reduce the risks of using valproate during pregnancy?

Patients not in specialist care taking valproate must be identified to allow counselling and planning of future care.

**Philip Smith, Association of British Neurologists (ABN), UK**

Question 1

What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?

Sodium valproate undoubtedly damages the unborn baby, increasing the risk of low intelligence and autism in children whose mothers took this medication in pregnancy. The Association of British Neurologists has been concerned for many years about women taking sodium valproate in pregnancy. Indeed, our members developed the world's first formal Epilepsy and Pregnancy Register, which has been highly influential in identifying and proving valproate's teratogenic risks.

Question 2

What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?

The Association of British Neurologists strongly supports the changes in labeling and the additional information provision for women taking this treatment. We emphasise that any woman who is taking valproate must know and understand the risks of becoming pregnant whilst taking this treatment. Yet, we also know changing to another treatment may bring its own problems.

Sodium valproate is the proven most effective treatment for generalised genetic epilepsies (the most common form of epilepsy in young people). Thus, young women who change medication from sodium valproate to different treatment risk having further seizures. This will result in loss of confidence, loss of driving eligibility and even loss of a job. Major seizures bring risks of injury and even of dying during a seizure. Furthermore, the DVLA advises UK drivers who change anti-epilepsy medication to stop driving until six months after the change is complete, even if remaining seizure free.

It is clear from the above that any woman making this change of medication will need a lot of information and support, from primary and secondary care.

Question 3

What other measures should be taken to reduce the risks of using valproate during pregnancy?

Women whose epilepsy is completely controlled on valproate are likely to be living full and normal lives, working and driving, often with little contact with specialist care. The major responsibility for informing women at risk from sodium valproate, and keeping them, is therefore with primary care (general practitioners and pharmacists) rather than specialist care.

## ***Sanjay Sisodiya, Epilepsy Society, UK***

For those with idiopathic generalised epilepsy, sodium valproate (SVA) can be one of the most effective treatments in all seizure types (absence, myoclonus and tonic clonic). However, due to its teratogenicity, SVA should be avoided, where possible, as a first line treatment in girls and women of childbearing age. Up to 40 per cent of babies exposed to SVA in the womb are at risk of developmental disorders, and up to 10 per cent are at risk of birth defects such as spina bifida or cleft palate.

However for some girls and women, SVA may be the only drug that will control their seizures, and seizures are not benign events. In some circumstances, tonic clonic seizures may cause miscarriage, trauma related to falls and blood conditions that can affect the developing baby - such as foetal hypoxia. The risk of SVA has to be assessed against the risk of seizures to both mother and baby.

We need to investigate demographically which groups of women and girls are not receiving the correct information about risks around sodium valproate. This could include young girls who may feel family planning issues are a consideration for the distant future rather than the present, and women whose epilepsy is controlled with sodium valproate and may not be having regular reviews.

At Epilepsy Society our genetic research is looking at the causes of epilepsy and also at each individual's response to different drugs. We are trying to establish whether a woman's genetic make-up or that of a developing foetus may determine response to a particular medication such as sodium valproate and the risk of being adversely affected.

It is essential that this research is accelerated, with necessary commitment and investment, in order to ensure that in the future, a simple genetic test will be able to assess the risk of having a baby with developmental or physical disorders, for all women who are taking sodium valproate.

***Dyfrig Hughes , Centre for Health Economics and Medicines Evaluation,  
Bangor University, UK***

Findings from: Marson A, et al. Defining patient preferences and priorities for treatment options and outcomes in epilepsy. NIHR Research for Patient Benefit Programme.

In response to Question 1 (what is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?) we will report the views of 103 women of childbearing potential who completed a web-based questionnaire , designed to value their preferences for seizure control and treatment-related adverse events, including the risk of foetal abnormality.

We found that patients valued a potential reduction in the risk of foetal abnormality greater than a potential increase in seizure control. A 1% increase in the probability of 12-month remission was of equivalent value to a 6% decrease in the possibility of foetal abnormality.

When results were combined with clinical trial evidence on monotherapy for generalised or unclassified epilepsy, we found that women of childbearing potential had a strong preference to avoid valproate. We modelled the utility women gained from being prescribed valproate, topiramate or lamotrigine. The utility for valproate was -0.02. This negative figure indicates women would prefer to avoid it. The most preferred alternative was lamotrigine.

Incorporating patient preferences changed the rank order of AEDs indicated by time to treatment failure in clinical trials. This was most significant for women of childbearing potential prescribed monotherapy for generalised or unclassified epilepsy, whose rank ordering was reversed from valproate > topiramate > lamotrigine observed in clinical trials.

This is independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0909-20161). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

***Paolo Martelletti, European Headache Federation (EHF), Department of Clinical and Molecular Medicine, Sapienza University, Italy***

Valproate is widely used in the prevention of migraine. Recent data confirms valproate teratogenicity and risk of hormone derangement. Valproate administration during pregnancy increases the incidence of major congenital malformations, reduces intelligence quotient and produce behavioral complaints. In females, we know that valproate use increases the risk of odd hormone pulse, weight gain, and polycystic ovarian syndrome. Despite EU guidelines recommending caution in the use of valproate for the prophylaxis of high frequency/pre-chronic/chronic migraine, this drug is still widely prescribed to reproductive-aged women and girls. In the presence of these well-documented scientific evidences the adherence to national and european guidelines calling for a warning in its use remains low. The warning on the prescription of valproate in migraine should be potentially extended from reproductive-aged or pregnant women also to fertile males. A Joint Statement between EMA and European Headache Federation (EHF) should be published in The Journal of Headache and Pain (EHF Official Journal) in order to minimize this risk and change the old-fashioned attitude of prescription. The incoming class of drugs, the monoclonal antibodies blocking CGRP(r) could be supportive for this educational purpose.

***Kim Morley, Epilepsy specialist midwife/ nurse practitioner, UK***

**Question 1 What is your view of the risks of taking valproate during pregnancy, including its potential effect on the child?**

Q1: As a practitioner specializing in the management of anti-epileptic drugs (AEDs), I have mixed views about the risks of valproate due to the potential devastating harm caused by pregnancy exposure versus lives destroyed and sometimes lost because of women not taking their AEDs or other AEDs not controlling their seizures.

I set up a unique specialist service 17 years ago to be a voice for women with epilepsy and to raise professional and public awareness about the potential teratogenic risks of drugs like sodium valproate. By effectively linking with other healthcare professionals, I have ensured women are correctly diagnosed with epilepsy and taking an antiepileptic drug regime that carries the least risk of harming their baby whilst protecting them from uncontrolled seizures. For the majority of women this holistic approach starts long before pregnancy is considered. Women are fully informed of potential risks from the available research evidence and empowered with their decision making in preparation of motherhood. Evidence demonstrates that women receiving this type of support are more likely to have healthy pregnancies and less likely to have adverse outcomes. It upsets me greatly when women become pregnant never having received this type of care; with modern communication this is unacceptable. Furthermore, if disclosure about risk is not handled by a knowledgeable practitioner, the consequences can be profound. This is because women instinctively put their baby's well-being before their own and this can lead to a sudden discontinuance of AEDs; very sadly, as identified in the maternal mortality reports, this can result in some pregnant women never getting to see their babies because they have died as a result of a convulsive seizure.

I have witnessed the profound effects of valproate syndrome on childhood development and behaviour and the challenges women face trying to obtain a diagnosis. This can deny children of appropriate proactive specialist support and impact further on their potential development. One woman was referred to me from another NHS Trust to gain support for her child who had severe fetal valproate syndrome. She said even though my ambition was to prevent this syndrome, she would never have tried an alternative AED or a lower dose of valproate; the risks to her were too great, but she did want to be a mum. She was so grateful that I had been the first person to offer her support; no-one would acknowledge that valproate caused her child harm. I have developed deep understanding of why some women choose to stay on valproate. As well as having to refrain from driving and the subsequent impact on quality of life, changing antiepileptic drugs can result in complete loss of seizure control, serious adverse effects, and very sadly in some cases, an increased risk of death. Motherhood itself raises a further dilemma for women if they are taking a drug like valproate because the consequence of a change of drug at this stage and a loss of seizure control could compromise their ability to parent safely.

Seeing children with valproate abnormalities including metopic craniosynostosis where the skull bones fuse prematurely, is extremely worrying. This condition in milder forms can go undetected but still impact seriously on neuro-development. How can we possibly know the extent of the adverse effects caused by valproate unless every child exposed to this drug in utero receives expert assessment and childhood follow-up?

**Question 2 What are your views on the measures currently in place to reduce the risks of using valproate during pregnancy?**

As one consequence of the measures in place there are now some young women with generalised epilepsy coming through transition whose lives have been destroyed by the cocktail of other AEDs

they have been prescribed without achieving seizure control. Invariably valproate has never been mentioned as an alternative because of the potential risks in pregnancy, yet it may be the only drug that will provide seizure control. One case a young girl was being home schooled as she was having clusters of uncontrolled convulsive seizures, problems with word finding and angry outbursts; her cognitive skills were reduced and she was at increased risk of sudden unexpected death in epilepsy. Following our joint specialist support, her four AEDs were gradually withdrawn and substituted for a low dose of valproate. An effective contraceptive device is in place; this young woman returned to school then college and is at university, seizure free. She has a boyfriend and is fully informed of possible adverse effects of valproate and the consequences of exposure in future pregnancy. She wants to achieve her goals before considering any changes and we will continue to support her on that journey to motherhood.

The measures in place will continue to fall short because of the lack of expertise in supporting women with epilepsy with prescribing decisions. AEDs are the most complex drugs to prescribe in the formulary; incorrect management can result in morbidity and mortality. Epilepsy services in the UK are fragmented due to lack of neurologists specialising in epilepsy, shortage of epilepsy specialist nurses, paucity of GP's with a specialist interest in epilepsy & lack of knowledge about epilepsy & the management of AEDs in maternity services. For the purpose of reducing this disparity, I provide expert advice to professional and charitable groups and have developed my own website [www.womenwithpilepsy.co.uk](http://www.womenwithpilepsy.co.uk) which showcases resources and information as a strategy to increase knowledge about risk assessment and reduction.

**Question 3 What other measures should be taken to reduce the risks of using valproate during pregnancy?**

The voices of thousands of women and families, represented by the speakers today are proof that more needs to be done to reduce the risks of valproate during pregnancy. It is imperative that women taking AEDs for any condition should receive a continuum of expert support to inform their decision making. As there is a shortage of professionals specialising in the management of AEDs, an expert European panel should be formed to guide professionals how to manage AEDs in women of child-bearing potential. I would be happy to be part of that panel.

Pharmacists have expert pharmaceutical knowledge and are in an optimal position to help increase knowledge about valproate risks. Providing additional training and funding for this group of professionals would be optimal in order they are all experts in AED medicines management and pharmacovigilance. Each time a woman of child-bearing potential collects her prescription there should be an additional check as to whether she has received the patient valproate guide and had the opportunity of a medication review. Pharmacists should be encouraged to refer all women of child-bearing potential taking valproate for preconception specialist support and provide information resources in an appropriate format about contraception, folic acid, risk assessment and medicines management.

**Angelika Wieck, European Psychiatric Association (EPA) / Greater Manchester Mental Health NHS Foundation Trust**

I am a consultant perinatal psychiatrist working in the perinatal mental health service of Greater Manchester, and an Honorary Senior Lecturer at the University of Manchester. I give 6 monthly Masterclasses on clinical reproductive psychopharmacology for the British Association for Psychopharmacology and teach reproductive psychopharmacology at the Annual Congresses of the European Psychiatric Association (EPA). I am the Chair of the Women, Gender and Mental Health Section of the EPA.

**The use of valproate for mental disorders:**

Valproate is recommended by NICE (2016)<sup>1</sup> for the treatment of acute mania and the prevention of bipolar episodes. In clinical practice, it is also often used for other mental disorders.

**Answer to question 1:**

My view is that there is overwhelming research evidence that valproate causes significant adverse effects to a large number of offspring during fetal development with long-term serious consequences to their physical, emotional, behavioural and cognitive development. Safe dose thresholds have not been sufficiently established for the different types of harm and co-medication with folic acid is unlikely to prevent harm in most children.

**Answer to question 2:**

Surveys (eg Wieck et al 2007<sup>2</sup>, Jones et al 2015<sup>3</sup>, Mukherjee et al, 2017<sup>4</sup>) have shown that adherence to guidance for valproate use by EMA, MHRA, and various NICE guidelines is unsatisfactory in clinical psychiatric practice. I expect, however, that the recent UK MHRA Patient Safety Alert (6 April 2017) with a clear list of actions to improve prescribing and a deadline for completion (6/10/17) will translate into significant progress. For example, the local Mental Health Trust and Medicines Management Committee are taking the suggested actions. However, in my view the MHRA guidance does not go far enough to prevent harm to unborn children of mothers with mental disorders.

**Answer to question 3:**

It is important to consider the use of valproate for mental disorders separately from the use for neurological disorders. This is because the place of valproate in the treatment for these conditions differs and this may or may not lead to different clinical guidance. The answer to this question here will therefore only cover mental disorders. There are effective alternative treatments to valproate for these conditions.

In my view, the risks to pregnancy arising from valproate use in mental disorders can be prevented by the following:

1. Valproate should not be prescribed to women who are pregnant, or are planning a pregnancy.
2. In psychiatry, valproate should only be prescribed to women of childbearing potential if they are also using highly effective and reliable contraception (long-acting reversible contraceptives).
3. Tools should be used that guide clinicians through treatment choices for women who are or could be childbearing, such as the treatment algorithm developed in Manchester.

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<sup>1</sup> National Institute for Health and Care Excellence (2016) Clinical Guideline 185

<sup>2</sup> Wieck et al (2007) Archives of Women's Mental Health, 10(2), 83-85

<sup>3</sup> Jones et al, Abstract, Annual Scientific Meeting, Royal College of Psychiatrists, 17 Nov 2015

<sup>4</sup> Mukherjee et al (2017) Abstract, International Congress, The Royal College of Psychiatrists, 26-29 June 2017

4. Further specific National guidance for clinicians should be developed for the following areas: a. The speed of valproate withdrawal should a pregnant woman taking valproate present to the clinician, b. The speed of withdrawal from valproate in women planning a pregnancy, c. alternative treatments to valproate for acute mania and long-term prophylaxis in bipolar disorder, d. Guidance on the use of long-acting reversible contraception.

## ***Giuseppe Capovilla, Italian League Against Epilepsy (LICE)***

- 1) As a chair of both an Epilepsy Center and a Child Neuropsychiatry Department, I want to confirm that the babies of women assuming VPA during pregnancy are at higher risk of having neurodevelopmental problems during their life.
- 2) The claimed relationship between the VPA dose and the occurrence of neurodevelopmental problems is too weak to be accepted. Indeed, instead of the daily dose, VPA blood level should be considered.
- 3) There is no scientific evidence of the superiority of VPA versus other treatments. In particular, there is no evidence that VPA is superior to topiramate to treat Janz syndrome, as evidenced in the paper published in *Epilepsia* (Glauser et al, 2013, see table 4) on behalf of the ILAE subcommission on AED Guidelines. In the SANAD paper, many methodological issues are present. VPA is an old drug. So, considering that the majority of the patients with Genetic (Idiopathic) Generalized Epilepsies are easily treated in monotherapy, and that VPA has been used for many decades, a false belief of its superiority could have been created among epileptologists. On the other hand, there is no evidence that TPM is superior to VPA, as evidenced in a recent Cochrane review (Liu et al, 2017) or that other drugs (lamotrigine, levetiracetam) are superior to VPA. So, independent studies should be encouraged to evaluate the comparative efficacy and effectiveness of VPA versus other drugs to treat Genetic (Idiopathic) Generalized Epilepsies, even if they should necessarily be planned only in males and this can constitute an important methodological bias.
- 4) Large independent epidemiological studies have demonstrated that all these drugs (TPM, LEV, LTG) have less probabilities to induce both malformations and neurodevelopmental problems in the babies of women assuming VPA during pregnancy.
- 5) The methodological method to produce the VPA mouse model of autism doesn't match perfectly with the human clinical condition. Indeed, it is obtained by the acute administration of an unique high VPA dose at a certain period of pregnancy. As a member of the Animal Model Working Group of the COMP, I suggest that studies evaluating the effects of chronic administration of VPA therapeutic dose should be planned in the animal model.
- 6) The measures are not sufficient. My opinion is that healthcare professionals are not fully aware of the (legal and medical) problems related to the inappropriate use of VPA. As the President of the Italian League Against Epilepsy, I have issued many official releases on the argument. Despite of this, too many female epileptic patients of childbearing potential continue to be unjustifiably treated with VPA as initial monotherapy and they are not adequately informed of the risks related to its teratogenicity.
- 7) The warning should be strengthened in the SmPC and an informative campaign should be conducted among the healthcare professionals

***Dina Popovic, Psychiatrist and clinical researcher, Israel***

I am a psychiatrist and clinical researcher with expertise in the field of Bipolar Disorder. I have practiced in Italy, Spain and Israel (where I am currently Head of Department of Psychiatry). I would like to compare the experience from different prescribing patterns and their impact on both the outcomes regarding Bipolar Disorder as well as safety issues.

***Ailsa McLellan, British Paediatric Neurology Association (BPNA)***

1) There is no doubt that sodium valproate can cause harm to babies whose mothers are exposed to the drug in pregnancy. The harm posed by valproate is more than for any other anti-epileptic drug for which good quality evidence is available.

2) From a paediatric perspective: In teenage and paediatric clinics currently the risks of valproate are highlighted to patients and families - and this information backed up with written information from MHRA and RCPCH. However, as paediatricians we are concerned that there is a presumption that all females, irrespective of age should be treated the same - and that some females, particularly those whose epilepsy may remit before puberty, do not have access to the most effective drug for their epilepsy as a first line treatment due to the current guidance about sodium valproate

3) Continuing to highlight risks to all our patients, particularly teenage patients and in transition is paramount to reduce the risk of teratogenicity - and BPNA members are committed to doing this

## ***Elisabeth Gnansia, Institut Européen des Génomutations (IEG)***

I am the first author of the first publication indicating a teratogenic effect of valproate, based on population data. The reference of this publication is : Robert E, Guibaud P. Maternal Valproic acid and congenital neural tube defects. Lancet, 1982, 2, 937.[I signed as E.Robert at that time]

In 1982 I was a researcher in the field of birth defects and a clinical geneticist. My proposal for the public hearing is to explain how I came to the idea that valproate was increasing the risk of spina bifida, and then how I followed up the topic in my research career, and how the publication was taken by the international research community on one hand, and the French Health authorities on the other hand.

I chair nowadays the scientific committee of the Lyon birth defects registry, and stay interested in clinical teratology. I read a number of articles in the lay press about the French lawsuit on valproate that started about 2 years ago. I have been interviewed by several persons (journalists, lawyer, politician, even environmental police), and many aspects of the question are to be revisited. I would like to share my experience about the different measures taken to prevent birth defects linked with valproate, to explain how the situation was 30 years ago and how it evolved. It is important (1) to address the problem of all anticonvulsants, the majority of whom increase the risk of developmental disorders, (2) to harmonize the diagnosis and treatment of patients needing antiepileptics. For these first two points, one should underline the importance of reassessing the indication of treatment. The doctor must consider the possibility to advise a drug free pregnancy in a selection of cases. Then a careful follow-up will check the possibility for the patient to have a regular life, avoiding all risks factors of seizure. (3) to establish procedures for follow-up of alarms in terms of side effects of drugs or exposures in general, with all necessary transparency and traceability. (4) to avoid attributing a posteriori to valproate all kind of unwanted effects in children exposed in utero (eg otitis, endocrine anomalies, pyloric stenosis).