



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Summary of the EMA public hearing on valproate in pregnancy

Public hearing held on 26 September 2017





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### Background information on the procedure

The European Medicines Agency (EMA) held a public hearing on 26 September 2017 in the context of an ongoing safety review looking at measures to reduce the risks of valproate medicines in pregnancy. The full recording from the public hearing is available [here](#).

Valproate medicines have been in use in EU countries since 1967. They are used to treat epilepsy, bipolar disorder, and in some countries to prevent severe migraine headaches. Because the medicines have been authorised individually in each country there are some differences in the way they are used from country to country.

EMA was asked in 2014 to recommend strengthened measures to minimise harm to babies born to mothers who were taking valproate. It had been known since its early use that if taken during pregnancy valproate can cause malformations in a developing baby, and more recent evidence, which led to the 2014 review, indicated that it may also affect brain development after birth.

In 2017, EMA was asked by a member state to review how effective its 2014 recommendations had been in minimising the risk of harm from valproate to unborn babies, and to see if more could or should be done to prevent or minimise harm. As part of this process, the Agency's experts in medicines safety, the Pharmacovigilance Risk Assessment Committee (PRAC), decided to hold a public hearing. The aim was to learn more directly from the different views and experiences of people who have taken valproate and those caring for such people.

The public was asked to consider a [list of questions](#) drawn up by the PRAC specifically for this public hearing, asking them to provide their views of the risks and the current measures to manage them, and for suggestions on how the latter could be strengthened.

### Summary of the public hearing

The total number of attendees was 65, including 28 patients and patient representatives, 19 healthcare professionals and academics, 11 from pharmaceutical industry and 7 from media. The hearing was also broadcast live on the EMA website.

Participants were welcomed by Guido Rasi, Executive Director of EMA, Linda McAvan, a member of the European Parliament who championed the legislation to permit such public hearings, and June Raine, chair of the PRAC, which is responsible for the review of valproate.



All three stressed that this was an important occasion and a further step in the commitment of EMA and EU legislators to ensure medicines regulation works ever more closely with patients and members of the wider public that it serves. The goal was for PRAC members to gather as wide a range of views as possible to support better regulation of valproate medicines across Europe and so the Committee was grateful for the wide range of participants.

Juan Garcia, EMA's Head of Public Engagement, explained the practical aspects of the hearing and Sabine Straus, PRAC member from the Netherlands, who heads one of the two expert teams leading the evaluation on behalf of the Committee, explained more about the procedure and how the information from all the participants would feed into the process.

The participants were then invited to share their insights, suggestions and advice. In order to make the best use of the time available and maximise the number of people able to participate, participants with views in common were asked to give a combined presentation where possible, with one speaker presenting their intervention – in each case, the speaker's name is given in **bold** in the list below. A written summary of each participant's intervention is available [here](#).

#### *Patients and affected families*

- Intervention 1
  - **Catherine Cox**, Fetal Anti-Convulsant Support Association, UK
  - Janet Williams, Independent Fetal Anti-Convulsant Trust (In-FACT) & FACS Syndrome Association, UK
- Intervention 2
  - **Marine Martin**, Association of Parents of Children with the syndrome anticonvulsant (APESAC), France
- Intervention 3
  - **Karen Keely**, FACS Forum, Ireland
- Intervention 4
  - **Clare Pelham**, Epilepsy Society, UK
  - Philip Lee, Epilepsy Action, UK
- Intervention 5
  - **Nathalie Raemdonck**, Belgian Association of Victims of Valproate Syndrome (ABVSV/ BVSVS), Belgium
- Intervention 6
  - **Martin Brodie**, International Bureau for Epilepsy (IBE)
- Intervention 7
  - **Josephine Tapper**, Patient, member of Bipolar UK
- Intervention 8
  - **Joanne Cozens**, Organisation for Anti-Convulsant Syndromes (OACS), UK
  - Emma Friedmann, FACSAWARE.NET, UK
  - **Branwen Mann**, Patient representing Anti-Convulsant Syndrome, OACS Youth Trustee

### *Pharmaceutical industry*

- Intervention 9
  - **Eric Teo, Sanofi**

### *Healthcare professionals and academics*

- Intervention 10
  - **Jurate Svarcaite**, Pharmaceutical Group of the European Union (PGEU)
- Intervention 11
  - **Helen Cross**, European Reference Network for Epilepsy (EpiCARE)
  - Timothy Barrett, University of Birmingham, UK
  - Daniel Hawcutt, Royal College of Paediatrics and Child Health (RCPCH), UK
- Intervention 12
  - **Torbjörn Tomson**, International League Against Epilepsy (ILAE) (CEA)
- Intervention 13
  - **Anthony Marson**, European Academy of Neurology (EAN)
  - Philip Smith, Association of British Neurologists (ABN)
  - Sanjay Sisodiya, Epilepsy Society, UK
  - Dyfrig Hughes, Centre for Health Economics and Medicines Evaluation, Bangor University, UK
- Intervention 14
  - **Paolo Martelletti**, European Headache Federation (EHF), Department of Clinical and Molecular Medicine, Sapienza University, Italy
- Intervention 15
  - **Kim Morley**, Epilepsy specialist midwife/ nurse practitioner, UK
- Intervention 16
  - **Angelika Wieck**, European Psychiatric Association (EPA)/ Greater Manchester Mental Health NHS Foundation Trust

### *Additional interventions*

As the time allowed for it, the Chair invited some additional interventions from the floor. Comments were provided by **Emma Friedman**, Marine Martin, Josephine Tapper, **Giuseppe Capovilla**, Anthony Marson, Karen Keely, Nathalie Raemdonck, **Elisabeth Gnansia**, and **Deborah Mann**.

Amongst the topics raised were: the possibility of translating effective information materials from a given member state into other EU languages; the need for more guidance for neurologists on withdrawal of women from valproate and transition to other antiepileptic drugs; the importance of doctors considering the implications in pregnancy in later life before starting the medicine in girls too young to be contemplating this; the impact of other possible long-term side effects including effects on DNA transcription and mitochondrial function in women who take the medicine; the need for cross-border collaboration between learned societies and professional organisations to identify best practice; the views of the experts on the relative value of antiepileptic drugs in various conditions and on how many other medicines should be tried in epilepsy or bipolar disorder before contemplating use of

valproate; whether treatment of male patients could affect their offspring; the role of genetics and individual variation in response to the risk-benefit equation; the need to consider the risks of the alternative treatments; and the importance of responsible prescribing and dispensing of valproate.

### *Summing up*

In summing up, the Chair noted how much the Committee had gained from the personal testimony of patients, families, and individuals exposed to valproate before birth and the insights that this testimony had offered.

With respect to the PRAC's first question, regarding the public's views of the risks of the medicine to the unborn baby if used during pregnancy, there seemed to be agreement that these were undeniable and well characterised. The views of the families and others on the seriousness of these and their impact on those affected had been powerfully and movingly conveyed. There had also been a comment about the possible risks of exposure in male patients and this was something the Committee would need to take away and think further about.

Secondly, the PRAC had asked the public to consider the effectiveness of current measures. Pretty much every speaker had confirmed that while much improved information resources had been developed in some member states after the PRAC's previous recommendations, these were simply not reaching the right people at the right time. Dissemination, implementation and acceptance of the need for change had not happened as had been intended, and so the hoped-for strengthening of risk minimisation had not been seen. As well as communication and knowledge there was a need to think about other ways to effect change. Things could not remain the same and it was clear that things can be done better.

In identifying how this could be achieved the PRAC's third question had been particularly fertile in generating responses. Speakers had provided important ideas, thoughts and suggestions with the highest and most altruistic of motives. The Chair noted that amongst the proposals and ideas from participants which the Committee would debate were:

- Strong support for a visible reminder of the risks on the outer packaging of valproate medicines; although previous PRAC discussions about a special symbol had identified some questions, this should be revisited in the light of the representations at the hearing
- Reminders of the need to ensure that every time valproate was dispensed women receive it in appropriate packaging accompanied by information and discussion of the risks; measures to ensure this happened needed support from pharmacists and the positive proposals from the profession were welcomed
- Alert prompts should be embedded in prescribing and dispensing software, to ensure the risks and the need for a discussion with patients were always flagged to healthcare professionals at the point of care (this would be optimal if linked to patient records, to ensure that caregivers were not swamped with inappropriate warnings)
- Regular (at least annual) reviews for all women receiving long-term valproate were supported, to ensure that their understanding of the risks and benefits was updated appropriately as their life plans change
- A record that women had been appropriately counselled regarding valproate risks was recommended, and might support busy healthcare professionals in carrying out this task regularly

- Registers of women who were receiving valproate and of children who had been exposed to valproate during pregnancy were supported
- Further development of professional education, so that all healthcare professionals were more aware of the risks associated with valproate use in pregnancy, was necessary
- A strong call for more coordinated care services at national level, to ensure individualised care plans for those affected (to the extent that the regulatory system as currently structured can influence this)
- There had been calls for public awareness and tools for public awareness campaigns should be examined

The Chair noted the need to think carefully about what could be done through regulatory tools and what needed other approaches. Some of the evidence provided raised contentious issues around requirements for informed consent. While some of the proposals were more straightforward for regulators to introduce than others, she stated that PRAC recognised the efforts the participants had made in providing their interventions and promised that every single point, spoken and written, would be reflected on by the Committee with great care.

Every view had been valuable, and the Committee was very grateful indeed to those who had attended, often from considerable distances and at some personal inconvenience, to help them strengthen the outcomes of the scientific review. The PRAC understood that the goal of those who had attended was to ensure that those who have used valproate or were currently using it, and those who will use it in the future, had their care informed by the best possible risk minimisation. In seeking to minimise risks now and into the future the Committee shared that common goal. The PRAC still needed to have further scientific discussions and to reflect on what it had been told during the hearing, so it would take a few more months before its conclusions were available. However, the most important thing was that we all get things right. In the meantime, a summary of the outcomes of the hearing [*this current document*] would shortly be made publicly available.

### **Next steps**

The PRAC will now continue its review, including further consulting stakeholders and scientific advisory groups, and will prepare a report on measures to reduce the risk of valproate-containing medicines during pregnancy and in women of childbearing potential, in accordance with the published timetable, available on the [procedure webpage](#). This report will set out the conclusions of the PRAC and will reference how the information gathered from stakeholders has informed the Committee's decision-making. This will include the interventions from the public hearing and any related written materials provided. The PRAC report will be fully published once the review is concluded.

All participants in the public hearing will be informed by EMA of the PRAC conclusions as soon as these are issued.

The final PRAC recommendation will be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) for adoption of a CMDh position/agreement. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

## Notes

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1. The legal basis for public hearings is Article 107j of Directive 2001/83/EC of the [pharmacovigilance legislation](#), which gives the PRAC the possibility to hold public hearings for safety reviews conducted by the Committee under Article 20 of Regulation (EC) No 726/2004, and Articles 31 or 107i of Directive 2001/83/EC.
2. Public hearings are held on a case-by-case basis, where the Committee determines that collecting the views of the public would bring added value to its review, in addition to the other channels of stakeholder engagement such as stakeholder submissions or through inclusion of patients and healthcare professionals in expert meetings.
3. Public hearings are conducted according to the [rules of procedure](#) for public hearings.
4. More information on the work of the European Medicines Agency can be found on its website: [www.ema.europa.eu](http://www.ema.europa.eu)

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