



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Public hearing on valproate: Account of events and outcomes

EMA, 30 Churchill Place London, E14 5EU
24 September 2018

12th Pharmacovigilance Stakeholder forum

Presented by Efstratia Vatzaki
Procedure management Department





Valproate

- **Valproate and related substances** (valproic acid, sodium valproate, valproate semisodium, and valpromide)
- Indications: Epilepsy, Bipolar disorder and prophylaxis of migraine (in some EU member states)
- Authorised via national procedures in all EU Member States, including Norway and Iceland
- Risks to the unborn child when valproate is used during pregnancy

* * * * *

For some patients with serious conditions, **valproate may be their only treatment option.**



Background: PRAC recommendations (Oct 2014) - restriction of use

- Valproate **should not be used** to treat **epilepsy** or **manic episodes of bipolar disorder** in girls, in women of childbearing potential (WCBP) and in pregnant women unless other treatments are ineffective or not tolerated. Women for whom valproate is the only option should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.
- In countries where valproate medicines are authorised for the **prevention of migraine**, women **must not** use valproate for preventing migraine when they are pregnant. Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.
- Additional Risk minimisation measures (RMMs) (Guide for prescribers, patient booklet, risk acknowledgment form), DHPC.
- Studies (Drug utilisation study and HCP survey) to assess effectiveness.



Background: several MSs - additional Risk minimisation measures (RMMs)

All RMMs recommended by PRAC

and

- Additional DHPCs
- Letters to prescribers and WCBP who had at least one valproate prescription in 2016
- Recommendations on alternatives to valproate in female children, WCBP and pregnant women treated for epilepsy or bipolar disorder
- Warning on the outer packaging
- Patient alert card
- Pictogram on the outer packaging



Background: France

Despite the implementation of the risk minimisation measures (RMMs) further to the finalisation of the PhV Article 31 referral in 2014, a national pharmacoepidemiological programme for all indications of valproate showed that in France there was a persistently high exposure to valproate among women of childbearing potential especially in the indication of bipolar disorder.

The **conclusion** of the French agency (ANSM), was that the RMMs that were implemented after 2014 were not enough to change the prescription patterns in this female population.

* * * * *

A **new EU review** was initiated by France for valproate in March 2017 specifically regarding the RMMs and their implementation.



Public hearing – chronology of events (before ...)

In March 2017 PRAC plenary meeting

- PRAC agreed that **Public hearing** should be organised
- Questions for:
 - LoQs to Companies
 - Written consultation with
 - Patients' organisations
 - HCPs' organisations
 - NUI to Member states



Public hearing – chronology of events (... during ...)

Patients, children affected, prescribing physicians, pharmacists, nurses, industry

- views on the risks if valproate is taken during pregnancy and effects on the child;
- views on the measures currently in place to reduce the risks of using valproate during pregnancy;
- What other measures could reduce the risks of using valproate during pregnancy.



Public hearing – chronology of events (... and after)

- Following the **Public hearing*** discussions further consultations with Clinicians and Stakeholders
 - Scientific advisory group (SAG) consultations
 - Neurology
 - Psychiatry
 - Discussions in the Working group on Quality review of documents (QRD)
 - Stakeholders meeting

* Public hearing [Summary](#) and [Written Interventions](#)



Outcome of the 2017 - 2018 EU review

- Contraindication for use **in pregnancy** for Bipolar disorders, Migraine prophylaxis and Epilepsy (unless there is no alternative treatment);
- Contraindication for use **in women of childbearing potential** in Epilepsy, Bipolar disorders and migraine, unless the conditions of Pregnancy prevention programme* (PPP)

* see [PRAC Assessment Report](#), for the detailed Pregnancy prevention programme text

Views and requests by the public vs. their implementation (1)

Materials

Request at PH	Outcome
Additional restrictions to prescription	Contraindications, Pregnancy prevention programme, initiation and supervision of treatment by specialists
Distribution of material	DHPC, Educational materials (Patient card, patient guide, HCP guide and Annual risk acknowledgment form)
Dispensing of medicine	Patient card on outer carton, smaller pack sizes, visual reminder
Tools for information campaigns	QR code
Websites	National competent authorities, Charities
Visual reminder	Strong recommendation for visual reminder, (national implementation)



Views and requests from public vs. their implementation (2)

Delivery of information to patients

Request at PH	Outcome
Regular re-assessment	Annual reassessment of patients
Alerts at dispensing	Patient card on outer carton
Record keeping on information dispensed	Recording of delivery of information
Professional training / awareness	Scientific publications <ul style="list-style-type: none">- Epilepsy*- Migraine**- Bipolar disorder (for submission)

* Kalviainen *et al*, 2018; The Lancet Neurology; [https://doi.org/10.1016/S1474-4422\(18\)30172-8](https://doi.org/10.1016/S1474-4422(18)30172-8)

** Vatzaki *et al*, 2018; The Journal of Headache and Pain; <https://doi.org/10.1186/s10194-018-0898-3>



Views and requests from public vs. their implementation (3)

Future legacy and monitoring

Request at PH	Outcome
New research	- Effect of valproate to offspring of a treated father and also in the third generation offspring (PASS)
Databases	- Register(s) on epilepsy and valproate including mothers and affected children

Other Studies

➤ Non-clinical studies

(transgenerational alterations of gene expression to the offspring, association between mitochondrial dysfunction and autism)

➤ Non-interventional studies

(DUS, surveys (x2), characterisation of the foetal anticonvulsant syndrome, switching of valproate in clinical practices)



Thank you - Any questions?

Efstratia VATZAKI, *PhD*

efstratia.vatzaki@ema.europa.eu

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555

Send a question via our website www.ema.europa.eu/contact

Follow us on  **@EMA_News**