From pregnancy to breastfeeding

Liana Gross-Martirosyan, MD, PhD, MPH
Alternate PRAC member
Medicines Evaluation Board, the Netherlands

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Pharmacovigilance: Involving the citizen
Porto

Background

- Pregnant or breastfeeding women are rarely included in clinical trials

- Data on safety in pregnancy for new medicines
  - Extrapolated from non-clinical data
  - Assumed based on pharmacological mechanism
  - Extrapolated from data from other medicines within the same class

- Safety during breastfeeding often based
  - on PK data
  - Known side effects seen in the user population
  - Information from other medicines within the class

Need for post-marketing monitoring

- For most new medications limited information available for prescribers on pregnancy/breastfeeding
  - Absolute or relative contraindications
  - *"Product may be used if benefits outweight risks"*
  - *"Only if clinically needed"*

- Therefore there are Risk Management Plans in place for all new medicines
  - Describe how the data on safety in pregnancy or breastfeeding will be collected post-marketing, eg studies
  - Describe how the risks in relation to use in pregnancy will be minimised in clinical practice, eg use of contraception

Sources of pregnancy and breastfeeding data post marketing

- Spontaneous reports by health care providers and patients
  - Obligatory for all medicines
  - Routinely collected and periodically analysed
  - Follow up questionnaires sent to the reporter
  - May provide information on specific patterns of malformations
  - Difficult to estimate increased risk

- Published literature
  - Clinical and epidemiological studies

- PK studies in breastfeeding women

- Dedicated pregnancy studies
  - Requested by regulators and conducted by companies
  - Often have comparator arm and can detect increased risk
  - Protocols carefully assessed for the right methodology

Post authorisation safety studies on pregnancy

- Major maformations have a rate of ~3% in general population
  - However the rate of specific malformations may be higher in specific populations, eg women with diabetes or other chronic conditions
  - Therefore comparison with rate in general population may not be valid
- The pregnancy studies should ideally have an internal comparator
  - Eg Women with diabetes taking drug X vs. women with diabetes not taking the drug

- Data sources:
  - Electronic medical records with mother/baby linkage
  - Pregnancy regsitries (eg antiretroviral pregnancy registry)
  - For some outcomes data with linkage with both mother and father medical records necessary (eg NDD) necessary

Post authorisation safety studies on pregnancy (2)

- Such studies may confirm the suspected risk in children exposed *in utero* or may provide evidence that the drug is safe in pregnancy

- Product information (SmPC) is updated with new information based on the study + updated advice for the prescribers

- If the risk is confirmed and the medicine is commonly used by women of child bearing potential, additional measures may be necessary besides contraindication
  - Advice on effective contraception, pregnancy tests before and during treatment, patient counselling etc.
  - These measures are sometimes called PPP (pregnancy prevention programm)

- Educational materials for health care providers and patients

Risks of valproate following in utero exposure

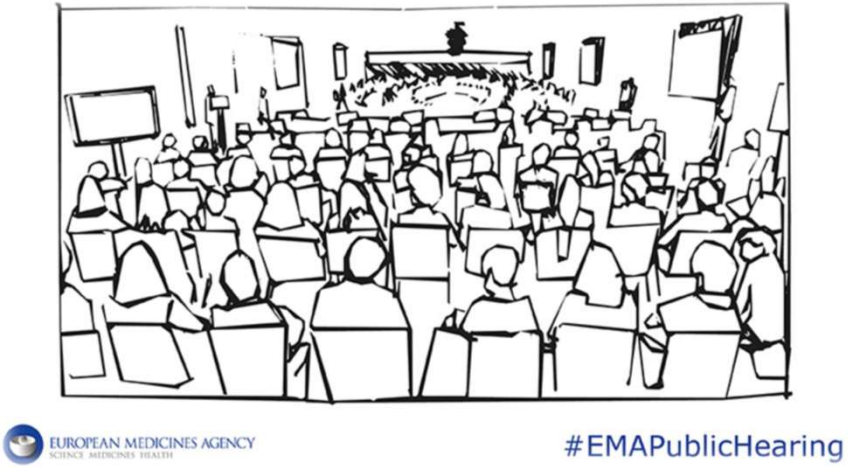
Monotherapy with valproate (vpa) results in:

- 10.7% of major congenital malformations
  - Neural tube defects, facial dysmorphysm, cardiac, urogenital malformations, deafness etc
- 30-40% neurodevelopmental disorders
  - Low IQ, speaking and walking delay, reduced verbal IQ and additional educational needs
- The risk is dose dependent however no safe dose

Public hearing

- **Engaging with patients and healthcare professionals** in the assessment of medicines

- What are your experiences with valproate and the existing risk minimisation measures

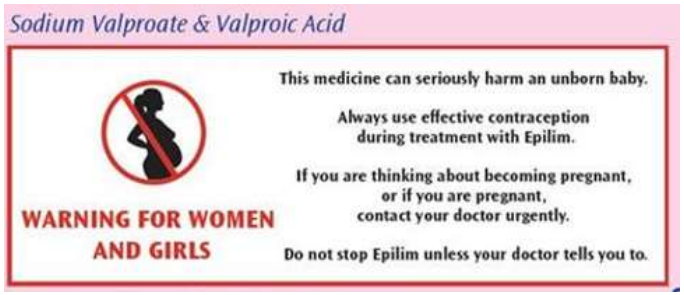


New measures implemented in 2018

- **Contraindication in women who can become pregnant if no effective contraception**
- **Contraindication in pregnancy**
- **Pregnancy testing before initiation of treatment**
  - Exclude pregnancy before starting vpa, and during treatment as relevant
- **Annual review** by specialist
- **Annual** (**signed) risk acknowledgement form**
  - At initiation of treatment and at annual reviews including F2F discussion
  - To re-enforce and document that a discussion of risks took place
- Broad target group for educational materials
  - Include neurologists, psychiatrists, GPs, pharmacists but also gynecologists, midwifes, teratology specialists

New measures implemented in 2018

- **"Visual reminder" on outer packaging**



- **Patient card**
  - Attached to the packaging
  - To support pharmacists' advising during dispensing
  - To increase awareness of teh patents on the risks and importance of contraception

New measures: QR code on the Package leaflet in all MSs

PACKAGE LEAFLET: INFORMATION FOR THE USER

Epilim® 100mg Crushable Tablets

sodium valproate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Is this leaflet hard to see or read?

Phone 01 4035600 for help

WARNING

Epilim, sodium valproate can seriously harm an unborn child when taken during pregnancy. If you are a female able to have a baby you must use effective method of birth control (contraception) without interruptions during your entire treatment with Epilim. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet.
Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.
Do not stop taking Epilim unless your doctor tells you to as your condition may become worse.

Other sources of information

For the most up to date patient information leaflet and important safety information on this product for girls and women of childbearing potential scan the QR code included in this leaflet with a smartphone. The same information is also available on the following URL: qr.epilimandme.ie

Patients should select the electronic patient information leaflet which matches the name of their medicine, the name of this medicine is stated in full at the beginning of this leaflet.

qr.epilimandme.ie

CONTAINS NEW INFORMATION

Valproate▼(Epilim)

prevent

valproate pregnancy prevention programme

Patient Guide for Women and Girls

This booklet is for you (or your parent/legal guardian) if you are a girl (of any age) or a woman of childbearing potential taking any medicine containing valproate (Epilim).

It is part of the valproate Pregnancy Prevention Programme, which aims to minimise the risks that could occur through the use of valproate during pregnancy.

Valproate (Epilim) can seriously harm an unborn baby. Always use effective contraception during your treatment. If you are thinking about becoming pregnant, or you become pregnant, talk to your GP straight away.

Do not stop taking valproate (Epilim) unless your doctor tells you to.

Electronic versions of this booklet and other materials related to the valproate Pregnancy Prevention Programme can also be found online at www.hpra.ie. Enter "Epilim" or "valproate" in the search box and then click on "Epilim" next to any of the medicines that appear.

…e keep this booklet. You may need to read it again.

THIS GUIDE WAS LAST UPDATED IN MAY 2018

▼This medicine is subject to additional monitoring. If you get any side effects, talk to your doctor. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See www.hpra.ie for how to report side effects.

AUTHORISED BY THE HPRA

Do these measures work in clinical practice?

Studies on effectiveness of new measures

- MAH and EMA funded studies
  - **Drug utilisation studies** to evaluate **prescribing behaviour** and effectiveness of RMM
    - Prescription of contraception
    - Pregnancy rates in women using valproate
  - **HCP and patient surveys** in >10 EU countries to evaluate **knowledge of the risks and measures** to avoid pregnancy exposure

Final remarks

- Limited pregnancy and breasfeeding data pre-authorisation
- Different data sources to collect safety data in these population post authorisation
  - Studies provide most robust pregnancy data

- It can however take a very long time before sufficient data is collected from pregnancy studies for analysis
  - Slow recruitment
  - Not many women using the product

- **Spontaneous reports from HCPs and patients remain a very important source of information and these are very valuable for us, thank you for reporting!**
  - Early identification of potential pregnancy adverse outcomes
  - Characterisation of patterns of malformations
  - Very useful source of information for breastfeeding

Thank you for your attention!!!!

Questions? @: ld.gross@cbg-meb.nl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