

**EMA Question**  
**VPA Risk Minimisation Measures**

**Inventory :**

Following the measures taken at the EMA in 2015 and 2017, APESAC communicated on these new measures on the media. TV programs have shown in 2017 that specialists weren't respecting the European recommendations and the new prescribing conditions, they continued to prescribe Valproate. The reason is that Valproate is a wide-spectrum anti-epileptic, and suitable for a lot of epilepsy patients. Today the use of valproate has decreased in France.

The only point of comparison we know is [England](#) : there were 17 pregnant women on sodium valproate in 6 months between October 2021 and March 2022. In France, we have 222 pregnant women exposed on sodium valproate in 2021.

***41% of the women who are surveyed are still treated with Depakine.***

In 2015 a **patient guide** was issued by the French Medicines Agency (ANSM). It costed 95,000 euros. Copies were sent to prescribers.

In November 2022, there was a re-edition of the patient guide which was sent to specialists. **Most women treated with valproate from the APESAC association didn't receive this patient guide.**

The prescribers print the **annual risk acknowledgment form** themselves, which they find on the website of the ANSM, as they don't receive a copy from the agency or the laboratories. They require the patients to sign it, but as they are the ones who print the document on their printer, they don't always give a copy to the patient.

According to the information we received about the form, some of the patients have signed it, but another group of patients doesn't know if they have received it or not, which raises questions about the notion of informed consent.

**The patient cards** aren't seen by the patients and even the pharmacists because they are integrated on the box, it's not visible.

**Pictograms**

***94% of the women who are surveyed think that the pictograms are useful.***

**APESAC Proposals:**

○ **Packaging Modification:**

- **Standardization of the message** on sodium valproate packaging.

In France it's written **Depakine + Pregnancy = PROHIBITED**. It would be normal to harmonize the information at the level of the member states. The French Health Agency has worked a lot on the subject with patients associations and the Ministry of Health could serve as a model. The sentence written in the rectangle should also be translated into all European languages :

"Do not use in girls, teenagers, women of childbearing age or pregnant women, unless other treatments have failed."

The terms used by France were the subject of close collaboration between the Ministry of Health, the Health Agency, and patient associations.

- The Pictogram, a **QR code** referring to digital information (on smartphone) but validated by the authorities. We can imagine a common information to all member states and translated. Normally, it can be required in the Marketing Authorization (MA) these requirements are transcribed in Annex II of the centralized in the Marketing Authorization.  
As the positive impact of the pictograms, it would be interesting to extend it to all teratogenic anti-epileptics, in particular for TOPIRAMATE, which has recently been the subject of a prescription re-evaluation in pregnant women.
- For drugs packaged in blister packs: slip a card into the box asking a simple question: are you aware of the serious risks to your unborn child from taking this drug?
- For medicines packaged in bottles: this message would be printed on the outside of the box lid and clearly visible when opened.

**Which measures have been taken?**

○ **Health authorities:**

- In France there has been no risk minimization campaign by the Health Agency, the only thing the ANSM proposed is [a small video of a testimony of a Depakine victim in 2022](#).
- The ANSM wrote in July 2022 to the hospitals of France to say that there were too many prescriptions of valproate.
- The ANSM also sent individualized letters to Valproate prescribers

**APESAC Proposals:**

- The ANSM should require that each valproate prescriber justify the reason for prescribing valproate to their patient of childbearing age.
- Measure to be taken: To do this, the Health Agency will have to check if the specialist has actually tried all the therapeutic alternatives from the health insurance. And if its not the case, a warning should be sent to him.

***80% of women surveyed agree with this proposal.***

○ **Patient organisations :**

- APESAC is the only patient association in France that informs about the dangers of Valproate in pregnant women and women of childbearing age. We had to ask the Ministry of Health to force the French association *Epilepsie France* to put on its website the EMA data regarding the dangers of valproate.

- We were the only ones to communicate on this problem. We used the national and regional press, TV shows in France and foreign countries. Also, the radio, social networks, podcast platforms and specialized press.
- A communication officer has been employed to inform about toxicity via graphic supports.
- A website has been created where the annual risk acknowledgment form can be downloaded, and a lot of information can be found about the dangers of anti-epileptic drugs in pregnant women.
- Special Depakine flyers have been sent individually to patients by post so that they can exchange with their specialist GP, newsletters are often sent to keep them informed of the risks of other anti-epileptic drugs, as well as the procedures for claiming compensation. Today, APESAC manages more than 8000 victims in France.
- We have also worked with the ANSM on the regular updating of data on the number of pregnancies on valproate, by asking them to have access to this data to reduce the number of prescriptions.

### **How were the victims informed?**

Most of the time, they tell us that it was thanks to a television program or a press article. For some time now, GP have been sending their patients to us.

The means of information that patients prefer to receive is always direct information from their specialist.

Here are <b>the proposals</b> made by APESAC for successful risk minimization
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- 1) **Prescription of Depakine or its derivatives validated by a second neurologist** : [As proposed by Great Britain, via the MHRA](#), the dispensing of Valproate should be done after validation by two neurologists who have tried all therapeutic alternatives. This double validation will prevent unscrupulous neurologists from continuing to prescribe it by habit.

There should be an ROSP (remuneration on objectives) to encourage GP to comply with their obligations to provide documents such as the patient guide.

***77% of women surveyed agree with this proposal.***

- 2) **Dispensing only in hospitals**, which would be authorized to prescribe and dispense Depakine and its derivatives in hospital pharmacies. I'm aware that this mean it will consider that the city pharmacist is less secure than the hospital pharmacist. However, there's a failure in the first line of treatment that justifies this consultation in hospital. The main flaw of this measure is that it complicates access to care.

***60% of women surveyed don't agree with this proposal.***

### **3) Compel health authorities to inform patients:**

- **Health insurance**: Send a letter, and/or an email and/or text to all women with epilepsy who are treated. This letter will contain general information on the conditions of prescription and delivery of Depakine. This information campaign will be regularly evaluated through surveys in order to measure the impact and relevance of this means of communication and information.

**95% of the women surveyed agree with this proposal.**

- Ministry of Health: Large-scale campaign financed by the Ministries of Health: each Member State should organize public campaigns:
  - Advertising campaigns on the topic of drugs and pregnancy.
  - Include this topic in school and university curricula.
  - Finance a TV series or an EU TV movie on the Depakine<sup>o</sup> affair.
  - To finance a comic book translated into all languages on the risks of drugs and pregnancy, including valproic acid.
  - To finance a MOOCs, "Massive Open Online Courses", that is to say an interactive training given online and open to all, by registration. This MOOC should be available via internet and smartphone on medication and pregnancy.
  - Develop the principle of a community tool in all the languages of the member states
  - Contraception: important! Encourage Member States to facilitate access to all forms of regular and emergency contraception, and to make it free.

**4) When Depakine and its derivatives are dispensed in pharmacies, the annual risk acknowledgment form must be scanned** in the same way as the Depakine prescription in order to obtain the drug.

94% of the women surveyed agree with this proposal.

- Concerning dispensing software (Pharmacists)

The recommendation to the member states could be to encourage the addition of a module in the Prescription Assistance Software (PAS) in connection with electronic prescribing, when it's deployed (France is among the latecomers; the generalization is announced for 2024).

- Proposals:

Member States should add to the remuneration of pharmacists from their margin on drug sales, remuneration for consulting missions. France has recently introduced a new service for pharmacists called "[paid pregnancy counselling](#)". We can envisage a generalized pregnancy interview mission in the EU for all women of childbearing age. We can also encourage all member states to introduce a specific paid service for pharmacists when valproate is dispensed.

#### **5)For laboratory:**

Producer laboratories should be obliged to publish the annual risk acknowledgment form, patient guide and send them to prescribers with reminder measures.