Information for pharmacists (city and hospital), neurologists, paediatric neurologists, paediatricians, general practitioners, psychiatrists, gynecologist, obstetrician gynecologist and midwives.

Valproate and derivatives: Potential risk of neurodevelopmental disorders in children whose father were treated with valproate or its derivatives within 3 months prior to conception.

The French National Agency for Medicines and Health Products Safety (ANSM) wishes to inform you of a study that suggests an increased risk of neurodevelopmental disorders in children whose fathers have been treated with valproate or its derivatives (**Depakine, Depakote, Depamide, Micropakine and generics**) within three months before conception, compared to fathers treated with other antiepileptics (lamotrigine or levetiracetam). This study has limitations which do not allow definitive conclusions to be drawn at this stage. The European Medicines Agency (EMA) has therefore requested additional analyses from the pharmaceutical companies in order to evaluate the robustness of these data. However, while waiting for their conclusions, we wish to share this information immediately **so that you can talk about this with your patients and take it into account if necessary.**

Men or adolescents treated with valproate or one of its derivatives:

- The use of these medicinal products in the three months prior to the conception of a child might expose this child to a potential increased risk of neurodevelopmental disorders.
- **Inform your patients of this potential risk.**
  - For those planning to have a baby, discuss with them the possibility of therapeutic alternatives.
  - Invite those who have conceived a child (already born or not) during their treatment, to put their questions to you in order to allow appropriate medical management.
  - Any parents who ask about possible developmental disorders of their child can be referred to the coordination and orientation platforms (PCO).
- **Inform your patients not to stop treatment on their own and the risks incurred if they stop treatment.**
- Discuss the necessity to introduce appropriate contraceptive measures.
- Tell them to notify that they are being treated with valproate or derivatives if they donate sperm.
- Provide them with the information sheet when prescribing or dispensing a medicinal product containing on valproate or its derivatives. Hard copies of this sheet will be sent to you in due course. In the meantime, we ask you to please print this information sheet, it is available on the ANSM website, or invite patients to read it online.

Reminder of the indications for valproate and its derivatives

- Depakine (sodium valproate or valproic acid) and its generics, as well as Micropakine (sodium valproate or valproic acid) are indicated for the treatment of epilepsy.
- Depakote (sodium divalproate) and its generic (Divalcote) as well as Depamide (valpromide) are indicated as second-line therapy in the manic episodes of bipolar disorder.

Study context

In 2018, after the European reassessment of the risk/benefit ratio of these medicinal products, pharmaceutical companies marketing these medicinal products were asked to conduct studies to better characterise the risks associated with taking them.

The objective of one of these studies[1] was to assess malformative and neurodevelopmental risks in children whose fathers had been treated with valproate or one of its derivatives before conception.

This study, conducted on the basis of several Scandinavian registries (Norway, Sweden and Denmark) over a long period of time, compared children whose father had been treated with valproate in the three months prior to conception with children whose father had been treated with lamotrigine or levetiracetam.

As a reminder in women

[1] https://www.encepp.eu/encepp/viewResource.htm?id=104938

Valproate (and derivatives) is an active substance with known teratogenic effects which carries a high risk of birth defects (11%) and neurodevelopmental disorders (up to 30 to 40%) in the event of maternal exposure during pregnancy. These medicinal products must not be prescribed to female patients except in cases of intolerance or inefficacy of alternative medicinal products.

For further information, consult the ANSM's thematic dossier on Valproate and its derivatives:
Dossier on the theme — Valproate and pregnancy — ANSM (sante.fr)

Report any adverse reaction you suspect to be linked to the use of valproate or its derivatives on signalement.social-sante.gouv.fr/.

Inscrivez-vous à la newsletter de l'ANSM : ANSM Actu (www.ansm.sante.fr)

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