Valproate (Depakine): New restrictions on use; pregnancy prevention programme to be put in place.

Direct healthcare professional communication

Date : February 2020

Dear Healthcare professional,

This letter is sent in agreement with Saudi Food and Drug Authority (SFDA) to inform you of **important new contraindications, strengthened warnings and measures to prevent valproate exposure during pregnancy.**

Summary

- **Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.**
- **Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and of congenital malformations (in approximately 10% of cases).**
- **In pregnancy and in women of childbearing potential new contraindications apply:**
    - **In epilepsy**
        - **valproate is contraindicated in pregnancy unless there is no suitable alternative treatment**
        - **valproate is contraindicated in in female children and women of childbearing potential, unless the conditions of the pregnancy prevention programme (described below) are fulfilled**

- **For women of childbearing potential currently using valproate the treatment may need to be re-evaluated to decide if the conditions of the pregnancy prevention programme (described below) are fulfilled.**

Key elements of the Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders, including the magnitude of these risks for children exposed to valproate in utero.

- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception, without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
- the patient understands the need to consult her physician as soon as she is planning a pregnancy to ensure timely discussion and switching to alternative treatment prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The product information of all valproate-containing products will be updated accordingly.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, a Patient Card (on the outer package), a Patient Guide, an annual risk acknowledgment form, and a Guide for prescribers, pharmacists and other healthcare providers involved in the care of women of childbearing potential using valproate will be available to inform healthcare professionals and patients/caregivers on the risks of valproate and the conditions for use.

A patient guide and patient card should be provided to all women of childbearing potential using valproate. An annual risk acknowledgement form needs to be used by the specialists at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Background information

In 2014 the warnings and restrictions on the use of valproate medicines in women and girls were strengthened, to minimise the risk of malformations and developmental problems in babies exposed to valproate in the womb. EMA's safety experts, the Pharmacovigilance Risk Assessment Committee (PRAC)

has now reviewed the impact of these measures following concerns that the measures were not sufficiently effective in increasing awareness and reducing valproate use appropriately during pregnancy. The PRAC found these concerns to be well founded and has therefore introduced new measures.

Risk of abnormal pregnancy outcomes

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is greater than when valproate is taken alone.

- The risk of congenital malformations is approximately 10%, while studies in preschool children exposed in utero to valproate show that in up to 30-40%, early development such as talking, and walking is delayed and they have low intellectual abilities, poor language skills and memory problems.[1],[2],[3],[4],[5]

Intelligence quotient (IQ) measured in a study of 6 year old children with a history of valproate exposure in utero was on average 7-10 points lower than children exposed to other antiepileptics.[6]

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.[7]

Limited data suggest that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).[8]

More detailed instructions related to the following topics are provided in the Annex of this letter:

the use of valproate in female children,
the need to rule out pregnancy before valproate initiation,
the use of effective contraception,
the annual treatment review by a specialist
the use of the annual risk acknowledgement form (at treatment initiation and during treatment review, at least annually),
what to do with valproate treatment at the time of pregnancy planning and during pregnancy
specific actions to be taken by the pharmacist such as provision of the patient card

Call for reporting:

- If you have any side effects, please contact :
  The National Pharmacovigilance Center (NPC)
- Fax: +966-11-205-7662
- SFDA Call Center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

Company contact point:
In the same time, Company pharmacovigilance team kindly request from you to report any suspected adverse events within 24 hours from your awareness through the following contacts:

Please contact: +966544284797,
Email: ksa_pharmacovigilance@sanofi.com

- For Medical Information:
- Please contact: +966 12 2219416
- Email:ksa.medicalinformation@sanofi.com

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