Sponsored by

SANOFI

Full prescribing information is available upon request: SANOFI, P.O. Box 9874, Jeddah 21423 K.S.A.,
Tel: +966-2-6693318, Fax: +966-2-6636191

For medical information and pharmacovigilance, please contact medical information line 0564095249
ksa_medical@sanofi.com, ksa_pharmacovigilance@sanofi.com

Version 1.1 dated 5.10.2017

KSA.VPA.15.11.44

Guide for Healthcare Professionals

This Guide is provided as part of the risk minimization measures developed for valproate to inform valproate prescribers of the risks associated with the use of valproate by women of childbearing potential and during pregnancy.

The Guide will provide up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

This guide should be used with the Patient information booklet. To learn more about valproate, please read the complete Summary of Product Characteristics before prescribing valproate.

SANOFI

WHAT YOU SHOULD KNOW ABOUT THE RISKS OF VALPROATE SODIUM / VALPROIC ACID USE IN FEMALE PATIENTS

VALPROATE contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders. These risks are briefly described below.

1. CONGENITAL MALFORMATIONS

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29), which represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show the risk is dose dependent. The risk is greatest at higher doses (above 1 g daily). A threshold dose below which no risk exists cannot be established based on available data

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

2. DEVELOPMENTAL DISORDERS

Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies[2-5] in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics[9]. Although the role of confounding cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

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

Treatment of female Patients with valproate

A. FEMALE CHILD FIRST PRESCRIPTION

After medical evaluation, you are considering prescribing valproate to your patient:

- Confirm that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).
- Discuss the following topics with your patient and relevant family members/care-givers:
  - Risks to pregnancy that are associated with the underlying condition;
  - Risks related to treatment, including risks related to valproate in case of pregnancy;
  - Need for an effective contraception method to avoid unplanned pregnancy.
  - Need for regular review of treatment
- Assess the most appropriate timing to provide advice on effective contraception methods and refer your patient to a specialist if needed.
- Ensure that your patient/family members/caregivers of the patient have understood the potential consequences in case of pregnancy and has/have an adequate level of understanding of the risks.
- A document has been developed to help you:
  - A Patient information booklet (Annex 1) which summarizes the teratogenic safety information and highlights key points for treatment management:
    - Read it, as it may help you to deliver appropriate information to your patient
    - Give one copy to your patient
- Keep in the patient's medical records.
- Advise your patient to contact you immediately
  - If she becomes pregnant or thinks she might be pregnant.
- Plan to review the need for treatment when she becomes capable of pregnancy.

B. WOMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING PREGNANCY

After medical evaluation, you are considering prescribing valproate to your patient:

- Confirm that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).
- Discuss the following topics with your patient:
  - Risks to pregnancy that are associated with the underlying condition;

- Risks related to treatment, including risks related to valproate in case of pregnancy;
- Need for an effective contraception method to avoid unplanned pregnancy.
- Need for regular review of treatment

- Assess the relevance of preconception counseling.
- Ensure that your patient has understood the potential risks to the child of using valproate during pregnancy and has an adequate level of understanding of the risks, and that she agrees to comply with the conditions for pregnancy.

  For this, the following document has been developed to support you:

  - A Patient information booklet (Annex 1) which summarizes the teratogenic safety information and highlight key points of treatment management
    - Give one copy to your patient
- Keep in the patient's medical records.
- Advise your patient to contact you
  - If she becomes pregnant or thinks she might be pregnant;
  - in case of any adverse events associated with her treatment.

C. WOMAN OF CHILDBEARING AGE WHO IS PLANNING PREGNANCY

- Remind your patients of teratogenic risks and risks of developmental disorders that can be seriously debilitating when taking valproate but also the risks of untreated seizures or bipolar disorder.
- Reassess the benefit/risk of valproate therapy, whatever the indication:
  - Consider if stopping treatment or switching to an alternative is possible.
  - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
  - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
  - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.
- Consider referring your patient to specialists for preconception advice.
- Ensure that your patient has understood the potential risks to the pregnancy, and has an adequate level of understanding of the risks
  - A Patient information booklet (Annex 1) should be given to the patient which summarizes the risks:
    - Give one copy to your patient
- Keep in the patient's medical records
- Advise your patient to contact their family doctor as soon as she becomes pregnant or thinks she might be pregnant in order to initiate appropriate pregnancy monitoring, including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

D. WOMAN WITH UNPLANNED PREGNANCY

- Schedule an urgent consultation with your patient to review treatment as soon as possible to reconsider the benefits and risks of valproate.
- Tell her to keep taking her treatment until you have seen her, unless you are able to give other advice based on your assessment of the situation.
  - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
  - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
  - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.
  - Ensure that your patient:
    - has truly understood the risks related to valproate in case of pregnancy
    - has received the Patient information booklet (Annex 1)
  - Keep in the patient's medical records.
- Initiate specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Summary

A. FEMALE CHILD FIRST PRESCRIPTION

1. Explain potential risks of the disease itself for the unborn child and the risks associated with use of sodium valproate in pregnancy
2. Assess your patient's need for treatment with sodium valproate
3. Inform your patient about the need to use effective contraception as soon as it is relevant
4. Ensure that your patient has received the Patient information booklet
5. Where applicable, advice your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.

B. Women of childbearing age who ARE not planning pregnancy

1. Explain potential risks of treatment and of untreated disease for the unborn child
2. Assess your patient's need for treatment with valproate
3. Inform your patient about the need to use effective contraception
4. Ensure that your patient has received the Patient information booklet
5. Advice your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.

C. Woman of childbearing age who is planning pregnancy

1. Explain potential risks of the disease itself on the unborn child, independent from valproate's own risks.
2. Re-assess benefit/risk of patient's therapy
3. Adapt current treatment
4. Advise your patient to contact you when she becomes pregnant or thinks she might be pregnant
5. Ensure that your patient has received the Patient information booklet

D. WOMAN WITH UNPLANNED pregnancy

1. Inform her to keep taking her treatment until you have seen her
2. Schedule an urgent consultation
3. Re-assess the benefit/risk of her therapy
4. Ensure that your patient has understood the risks related to valproate in case of pregnancy
5. Ensure that your patient has received the Patient information booklet

For PV reporting:

Collecting data of patient exposure to Depakine during pregnancy and breast feeding "with or without adverse event" are very important in the continuous safety profile evaluation of the products, therefore, PV team kindly request from HCPs to report these data within 24hours from their awareness to ksa_pharmacovigilance@sanofi.com.

In the same time, kindly find below box contains National Pharmacovigilance and Drug Center (NPC) contacts to report any side effect.

To report any side effect (s):

National Pharmacovigilance and Drug Safety Center (NPC)

Fax: + 966-11-205-7662

Tel.: +966-11-2038222

Ext.: 2356-2317-2354-2334-2340-2353

Toll-free: 8002490000

E-mail: npc.drug@sfda.gov.sa

Web: www.sfda.gov.sa/npc

REFERENCES

1. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81(1):1-13.
2. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October;51(10):2058-65.
3. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96:643-647
4. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009;360 (16): 1597- 1605
5. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236
6. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J,Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52
7. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013;309(16):1696-1703
8. Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. Epilepsy Behav. 2011; 22(2):240-246