Important Information for Healthcare Professionals on the Risks of Valproate▼ in Female Patients

This booklet must be read before considering prescribing valproate. It is provided as part of the risk minimization measures developed to inform prescribers of the risks associated with the use of valproate by females of childbearing potential and during pregnancy.

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▼ This medicinal product is subject to additional monitoring.

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

Adverse event reporting

Adverse events should be reported. Reporting forms and information can be found at **www.mhra.gov.uk/yellowcard**

Adverse events should also be reported to the Sanofi drug safety department on **01483 554242**, or to the relevant manufacturer of the product if not Sanofi.

What you should know about the risks of 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 women with epilepsy 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 1g 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 antiepileptic drugs[6]. 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, if you are considering prescribing valproate to your patient:

✓ Confirm that treatment with valproate is appropriate for your patient (i.e. alternative treatments are ineffective or not tolerated).

✓ 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 when used in 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 when used in pregnancy and has/have an adequate level of understanding of the risks.

✓ Give a copy of the Patient Guide to your patient

✓ Complete the checklist with your patient and keep a copy in the patient's medical records.

✓ Advise your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant.

✓ Plan to review the need for treatment when she is able to become pregnant.

B. Woman of childbearing age who is 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. alternative treatments are ineffective or not tolerated).

✓ 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 when used in pregnancy;
- Need for an effective contraception method to avoid unplanned pregnancy;
- Need for regular review of treatment.

✓ Assess the relevance of preconception counselling.

✓ 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 understands the importance of using contraception to avoid unplanned pregnancy.

✓ Give a copy of the Patient Guide to your patient.

✓ Complete the checklist with your patient and keep a copy in the patient's medical records.

✓ Advise your patient to contact you:

- if she thinks she might be pregnant or becomes 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 during pregnancy 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 appropriate.
- 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.

  There is no dose threshold considered to be without any risk but the risk of birth defects and developmental disorders is higher at greater doses.
- 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 there is some evidence that it does not reduce the risk of birth defects associated with in utero valproate exposure.

✓ Refer 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.

✓ Give a copy of the Patient Guide to your patient.

✓ Complete the checklist with your patient and keep a copy in the patient's medical records.

✓ Advise your patient to contact their family doctor and specialist as soon as she thinks she might be pregnant or becomes 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.

✓ Explain why she should continue with 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.

✓ Ensure that your patient:

- has fully understood the risks related to valproate and consider further counselling.
- has received the Patient Guide.

✓ Complete the checklist with your patient and keep a copy in the patient's medical records. This record is the opportunity to assess whether the patient has fully understood the risks.

✓ 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 as well as the future risks for the unborn child and the risks associated with use of valproate in pregnancy
2. Assess your patient's need for treatment with 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 Guide
5. Where applicable, advise your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant.

B. Woman of childbearing age who is 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 Guide
5. Advise your patient to contact you immediately if she thinks she might be pregnant or becomes 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. Reassess benefit/risk of patient's therapy
3. Adapt current treatment
4. Advise your patient to contact you if she thinks she might be pregnant or becomes pregnant
5. Ensure that your patient has received the Patient Guide.

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 and consider counselling
5. Ensure that your patient has received the Patient Guide.

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5. Thomas SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour.* 2008 (13):229–36.
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8. Cohen MJ et al. Fetal antiepileptic drug exposure: motor, adaptive and emotional/ behavioural functioning at age 3 years. *Epilepsy Behav.* 2011;22(2):240–46.

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