This summary guide must be read before considering prescribing valproate. It 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. For further detailed information please refer to the Health Products Regulatory Authority (HPRA) website: www.hpra.ie and Sanofi website: www.sanofi.ie.

Sodium valproate should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate.¹

This guide should be used in conjunction with the patient information booklet and the prescriber/patient checklist.

The prescriber/patient checklist will help ensure that you and your patient/carer have a full discussion of the key information, risks and risk minimisation measures and that your patient/carer fully understands these.

To learn more about valproate, please read the complete Summary of Product Characteristics before prescribing valproate.

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%.² 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, craniosclerosis, 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 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.³⁶

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.⁷ 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.³

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).⁹

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/carer:
  • The 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.
  • The need to use effective contraception as soon as it is relevant and refer to a specialist if needed.
  • The need for regular review of treatment.
✓ Ensure your patient/family member/carer understands the potential consequences when used in pregnancy and has/have an adequate level of understanding of the risks.
✓ Ensure that your patient has received the patient information booklet.
✓ Complete the prescriber/patient checklist with your patient and keep a copy in the patient’s medical records.
✓ Plan to review the need for treatment when she reaches puberty.
✓ Where applicable, advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.

B. Woman of childbearing age who is not planning pregnancy

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:
  • The potential risks of treatment and of untreated disease for both the woman and the unborn child.
  • The potential risks to the unborn child if used in pregnancy and has an adequate level of understanding of the risks.
✓ Assess the relevance of preconception counselling.
✓ Ensure that your patient has received the patient information booklet.
✓ Complete the prescriber/patient checklist with your patient and keep a copy in the patient’s medical records.
✓ Advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.
✓ Advise your patient to contact you in case of any adverse events associated with her treatment.
C. Woman of childbearing age who is planning pregnancy

✓ Remind your patient of the 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, please refer to Sanofi’s Valproate Guide for Prescribers for information on adapting current treatment: http://www.sanofi.ie/l/ie/en/layout.jsp?cnt=531D57BC-EABC-491D-ADF6-DEED1483A433.

✓ Explain potential risks of the disease itself on the unborn child, independent from valproate’s own risks.

✓ Ensure that your patient has understood the potential risks to the pregnancy, and has an adequate level of understanding of the risks.

✓ Ensure that your patient has received the patient information booklet.

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

✓ Refer your patient to specialists for preconception advice.

✓ Advise your patient to contact you and her specialist when 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 an unplanned pregnancy

✓ Inform the patient to keep taking her treatment until you have seen her.

✓ Schedule an urgent consultation with your patient to review treatment as soon as possible to reconsider the benefits and risks of valproate.
  • If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, please refer to Sanofi’s Valproate Guide for Prescribers for information on adapting current treatment: http://www.sanofi.ie/l/ie/en/layout.jsp?cnt=531D57BC-EABC-491D-ADF6-DEED1483A433.

✓ Ensure that your patient has understood the risks related to valproate in case of pregnancy and consider further counselling.

✓ Ensure that your patient has received the patient information booklet.

✓ Complete the prescriber/patient 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 specialised prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Patient information cards for girls and women of childbearing age are available from pharmacists. These cards complement the valproate patient information booklet.
It is recommended that pregnancies where the women are taking valproate for epilepsy are enrolled in the Irish Epilepsy and Pregnancy Register. For further information on the Irish epilepsy and pregnancy register and for information on how you can register a pregnancy please see www.epilepsypregnancyregister.ie or Freephone 1800 320 820.

Please remember that any suspected adverse reactions should be reported to the HPRA via HPRA Pharmacovigilance, Earlsfort Terrace, Dublin 2; Tel: 01-6764971. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

This summary guide has been complied using information from Valproate Guide for Prescribers available at www.sanofi.ie.

REFERENCES


