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Medicines related to valproate: risk of abnormal pregnancy outcomes

Dear Healthcare professional,

This letter is to inform you of important new information and strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid [brand leader: Epilim] and valproate semisodium [brand leader: Depakote]), following completion of a Europe-wide review.

Summary

- **Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases)**
- **Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.**
- **Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.**
- **Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.**
- **You must ensure that all female patients are informed of and understand:**
  - **risks associated with valproate during pregnancy;**
  - **need to use effective contraception;**
  - **need for regular review of treatment;**
  - **the need to rapidly consult if she is planning a pregnancy or becomes pregnant**

Please refer to the General Medical Council's consent and prescribing guidance.

Further information on the safety concern and the recommendations

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 up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems[1,2,3,4,5].
- Intelligence quotient (IQ) measured in a study of 6 years old children with a history of valproate exposure in utero was on average 7-10 points lower than those 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
- Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD) [7,8,9].

Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of child-bearing potential unless clearly necessary i.e. in situations where other treatments are ineffective or not tolerated.

Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.

If you decide to prescribe valproate to a woman of child-bearing potential, she must use effective contraception during treatment and be fully informed of the risks for the unborn child if she becomes pregnant during treatment with valproate.

Treatment during pregnancy

If a woman with epilepsy or bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments.

If valproate treatment is continued during the pregnancy:

- the lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment forms;
- Initiate specialised prenatal monitoring in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformations.

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[9] 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

- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Further information

A dose-related risk of developmental disorders was reported for valproate in six of the 28 studies included in a Cochrane review.[10] However, based on the available data, it is not possible to establish a threshold dose below which no risk of developmental disorders exists. The available data suggest that the risk of developmental disorders may apply to valproate taken at any stage of pregnancy.

The product information will now be updated to reflect our current understanding of the available evidence and to make information as clear as possible.

Educational materials (guide for healthcare professionals, patient information booklet) are in Annexe 1 and 2 of this letter. These are to inform healthcare professionals and patients about the risks associated with valproate in female children, female adolescents, women of childbearing potential and pregnant women.

Call for reporting

Valproate is now a black triangle medicine and is subject to additional monitoring. Therefore please report **any** suspected side effects to valproate via the Yellow Card scheme (www.gov.uk/yellowcard).

Yours sincerely,

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Annexe 1: Guide for Healthcare professionals

Annexe 2: Patient information booklet

[10] Bromley R, Weston J, Adab N et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014, Issue 10

Annexe 1: 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 in conjunction with the Patient information booklet. 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%[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].

One study 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. in situations where 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 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.

    - Give a copy of the patient information booklet to your patient
- 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. in situations where 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 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.
    - Give a copy of the patient information booklet to your patient

- 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
    - Give a copy of the patient information booklet to your patient

- 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 2)
- 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, advise 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. **Advise 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**

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Annexe 2: Patient Information booklet

PATIENT BOOKLET –VALPROATE

The information in this booklet is for women who are being prescribed valproate and are able to get pregnant (of child-bearing age). Read this leaflet along with the patient information leaflet which comes in the medicine box and if you have any questions talk to your doctor or pharmacist.

There is a lot of information and it is recommended that you show this booklet to friends and family to help you discuss and understand your treatment. This booklet was last updated in January 2015.

Keep this booklet. You may need to read it again.

RISKS TO THE UNBORN CHILD

Valproate can be harmful to unborn children when taken by a woman during pregnancy.

Whether taken on its own or with another epilepsy medicine, valproate seems to carry a higher risk if taken during pregnancy than other epilepsy medicines. The higher the dose, the higher the risks but all doses carry a risk.

It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.

If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in ever 100 born to women who don't have epilepsy.

It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.

Autistic spectrum disorders and childhood autism are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to be at risk of developing symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.

Before prescribing this medicine to you, she or he will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- **Make sure you are using an effective method of contraception**
- **Tell your doctor at once if you are pregnant or think you might be pregnant.**

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- **Make sure you are using an effective contraception**
- **Tell your doctor at once if you are pregnant or think you might be pregnant.**

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should discuss with your doctor well before you become pregnant so that you can put several actions in place so your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may need to change the dose of valproate or switch you to another medicine before you start trying for a baby. If you become pregnant, you will be monitored very closely both for the management of your epilepsy/ bipolar disorder as well to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- **Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/ bipolar disorder is controlled and the risks to your baby are reduced**
- **Tell your doctor at once when you know or think you might be pregnant.**

AN UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been treated with valproate are at risk of birth defects and problems with early development which can be debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your epilepsy/ bipolar disorder medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- **Tell your doctor at once if you know you are pregnant or think you might be pregnant.**
- **Do not stop taking valproate unless your doctor tells you to.**