28.11.2014

Medicines related to valproate: risk of abnormal pregnancy outcomes

Dear Healthcare professional,

This letter is sent in agreement with European Medicines Agency (EMA) and The Medicines Authority to inform you of important new information and strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid, valproate semisodium and valpromide), 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.**
- **Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy.**
- **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**

<u>Further information on the safety concern and the recommendations</u>

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].

[1] Meador K, Reynolds MW, Crean S et al. 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.

- 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 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 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.
- 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.

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

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[2] Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, Liporace JD, Sam M, Kalayjian LA, Thurman DJ, Moore E, Loring DW; NEAD Study Group. Antiepileptic drug use in women of childbearing age. Epilepsy Behav. 2009;15(3):339-43.
[3] Bromley RL, Mawer G, Clayton-Smith J, Baker GA; Liverpool and Manchester Neurodevelopment Group. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology. 2008;71(23):1923-4.
[4] Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children of mothers with epilepsy. Epilepsia. 2007 Dec;48(12):2234-40.
[5] Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011 July;96(7):643-7.
[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;12(3):244-52.
[7] Christensen J, Grønborg TK, Sørensen MJ et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013; 309(16):1696-703.
[8] Cohen MJ, Meador KJ, Browning N, May R, Baker GA, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD study group. Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6years. Epilepsy Behav. 2013;29(2):308-15.
[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

Educational materials will be made available to healthcare professionals and patients in order to inform about the risks associated with valproate in female children, women of childbearing potential and pregnant women.

Call for reporting

Any suspected adverse events should be reported to Sanofi Malta Ltd., 3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022; fax: 21493024

This medicinal product is subject to additional monitoring.

Alternatively any suspected adverse reactions can also be reported to
Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: www.medicinesauthority/adrportal.

Company contact point
If you have any questions or require additional information, please call Medical Information Services at Sanofi-Aventis Malta Ltd, 3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, Fax: 21493024

Annexes

Relevant sections of the Product Information that have been revised

Section 4.2 Posology and method of administration
[…]
Female children, female adolescents, women of childbearing potential and pregnant women <Invented name> should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably <invented name> should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.

Section 4.4 Special warnings and precautions for use

[…]

Female children/Female adolescents/Women of childbearing potential/Pregnancy:

<Invented name> 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. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with

<invented name> plans a pregnancy or if she becomes pregnant.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of <invented name> during pregnancy (see section 4.6).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.

Section 4.6 Fertility, pregnancy and lactation
[…]
<Invented name> should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated.
Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

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). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor and major malformations. 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.

Developmental disorders
Data have shown that 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.
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.
Although the role of confounding factors 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.
Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).
Female children, female adolescents and woman of childbearing potential (see above and section 4.4)

If a Woman wants to plan a Pregnancy
• During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
• In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed
• In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.
Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:
- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.
- 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.
- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Risk in the neonate
- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors.

Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding
Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from <invented name> therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8).
Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

Section 4.8 Undesirable effects
Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

[…]

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.