SANOFI

Date: 14-JUN-2015

Subject: Medicines related to valproate / DEPAKINE®: risk of abnormal pregnancy outcomes

Dear Healthcare professional,

This letter is sent in agreement with Saudi Food & Drug Authority (SFDA) to inform you of important new information and strengthened warnings related to safety of medicines related to valproate / Depakine (sodium valproate, valproic acid, valproate semi sodium and valpromide),.

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.**
- **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**

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 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 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;

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[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.
[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

- 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.

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

- **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**

This medicinal product is subject to additional monitoring therefore any follow-up information / outcome should be reported to NPC as mentioned above.

Company contact point

In the same time, Company pharmacovigilance team kindly request from you to report any suspected adverse events within 24 hours from your awareness through the following contacts:-

- **Fax: + 966-11-4627914, + 966-12-6636191**
- **Tel.: + 966-11-4633190, + 966-12-6693318**
- **Mobile: + 966 56 4095 249**
- **E-mail: ksa_pharmacovigilance@sanofi.com**

Sherif Waguih, *M.D., M.Sc.*
Director Medical Affairs

Signature
Date: 14 June 2015

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Saudi Arabia