Notification of a Referral under Article 31 of Directive 2001/83/EC.

This notification is an official referral under Article 31 of Directive 2001/83/EC made by the United Kingdom to the PRAC

Administrative details

Product Name (s), is appropriate, Strength(s) and Pharmaceutical Form (s)	Substances related to valproate (e.g. sodium valproate, valproic acid, valproate semisodium, valpromide), all strengths, all pharmaceutical forms
Applicants(s)/Marketing Authorisation Holder(s)- In the referring member state.	Various MAHs including Sanofi, Destin Pharma, Wockhardt, Zentiva

Valproate has been authorised for several decades across the European Union for the treatment of epilepsy. It is also authorised for the treatment of the manic phase of bipolar disorder and prevention of migraine headaches in some member states.

Epilepsy is a serious neurological condition and it is important that is treated effectively including during pregnancy. It is widely recognised that women who take antiepileptics during pregnancy have a higher risk of having a child with a birth defect than women in the general population - this risk is estimated to be 2-3 times higher. The likelihood of having a child with birth defects is further increased if the woman takes more than one antiepileptic medicine during pregnancy. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than with some of the other antiepileptic drugs. This risk is clearly reflected in the valproate product information provided for patients and prescribers. The UK product information also contains some information on the association between fetal valproate exposure and longer term neurodevelopmental delay in the child, including a link with autism spectrum disorder

In 2009, there was also a European review of the safety and effectiveness of valproate in the treatment of manic episodes in bipolar disorder. This review considered the teratogenic risk associated with use of valproate in pregnant women and also examined the potential for delayed intellectual development in the child. At this time it was not clear whether adverse neurodevelopmental effects would improve with time or be more enduring or what the gravity of impact of various maternal confounders might be on the observed increased risk and this uncertainty remains reflected in the current information in many member states, including the UK.

In recent years, results of further studies have emerged which have improved our understanding and allow us to better characterise the risk of the longer term potential neurodevelopmental effects following *in utero* exposure to valproate. These studies have highlighted that in some children the effects appears to persist and manifest as a range of neurodevelopmental abnormalities and autism spectrum disorder. These emerging data also suggest that the risk of neurodevelopmental delay and autism spectrum disorder may be independent of maternal confounders [1-4].

Product information appears to differ across the European Union and there is a need for further revisions in order to bring it in line with all currently available evidence. The most recent data on neurodevelopmental delay and autism spectrum disorder associations with foetal valproate syndrome also call for a re-evaluation of the benefit risk of valproate where safer alternative treatments are available in particularly in relation to use in migraine prophylaxis and bipolar disorder management.

Whilst there are existing warnings in the valproate product information it is not considered to fully reflect the most recent evidence from the emerging studies, which have not identified a new safety concern per se but have clarified the magnitude and nature of the risk and suggest that the risk of neurodevelopmental delay is greater than previously thought. Therefore, there is a need for further review to ensure appropriate risk minimisation measures are in place to help optimise safe use and reduce the risk associated with use during pregnancy.

In light of the above, and given widespread use of valproate in different indications, the UK considers that it is in the interest of the Union to refer valproate containing products to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether the new data impacts on the balance of benefits and risks of valproate in all of its authorised indications and whether marketing authorisations should be maintained, varied suspended or withdrawn.

A draft list of questions to be submitted to the MAHs is annexed

Signed

[redacted]

Dr Ian Hudson

Chief Executive

Date

7th October 2013

References

1. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kennedy A, Lip race JD, Pennell PB, Privateer M, and Luring DW. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD Study): a prospective observational study. *Lancet Neurology*. 2013, March;12(3): 244-252.

2. Bromley R et al. The prevalence of neurodevelopment disorders in children prenatally exposed to antiepileptic drugs. J Neural Neurosurgery Psychiatry 2013; 0: 1-7

3. Christensen J et al. Association of sodium valproate with Risk of Autism Spectrum Disorders and Childhood Autism. JAMA, April 24, 2013. Vol 309, No 16.

4. Veiby, Gyri et al. Exposure to antiepileptic drugs in utero and child development: A prospective population-based study. Epilepsia. 2013. Aug; 54(8): 1462-72

Annexe - Draft list of questions

Question 1

The MAHs should provide information on the following:

1a. The current marketing status in the European Union including information related to all indications. In addition, MAHs should clearly indicate for which country a specifically dedicated presentation has been granted for a particular indication.

1b. The posology, treatment duration, contraindications, warnings and precautions and undesirable effects included in the summary of products characteristics (SmPC) and the package leaflet regarding the risk of use during pregnancy. Main differences between SmPCs/PLs in the different EU Member States should be tabulated as indicated in the appended tables.

1c. The estimated patient exposure in the different EU Member States for all indications. This exposure information should provide the following, if available:

i) use in women of child bearing potential (women between 15 and 49 years) by country;
ii) information on treatment indication, dose and duration of use.

Question 2

The MAHs should provide an analysis of all available safety data relevant for each indication. These analyses should include comprehensive cumulative reviews of data from clinical trials (including both MAH sponsored and non-sponsored studies), pharmacoepidemiological studies, including any pregnancy registries and published literature.
The analysis of available data should have a particular focus on the risk of neurodevelopmental delay and autism spectrum disorder and examine:

i) evidence for a biological basis for the aetiology of the neurodevelopmental effects and autistic spectrum disorder, including the specific difference among study outcomes concerning differences in effect on verbal and non-verbal abilities.
ii) the effects of maternal confounders on the neurocognitive outcomes of the child with special emphasis on- maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Question 3

The MAHs should provide an assessment of the benefit/risk balance of their product in all licensed indications. Based on European or international recommendations, the place of valproate containing products among the currently available therapeutic armamentarium for the authorized indications should be discussed.

Question 4

4 a) The MAHs should provide details of any specific measures that have already been taken in order to minimise the risk of unintended and intended pregnancy exposures and comment on the impact of such measures.

4 b) The MAH should comment on how well the current product information for sodium valproate reflects the latest data and suggest proposals of how these latest data may be reflected in the labelling (SmPC, PIL).

4 c) In addition, the MAHs should consider additional proposals for any complementary measures to further minimise the risks of fetal valproate syndrome including changes to the SmPC and package leaflet.

Appendix 1

INNs	Product name	Indication(s)	Type of marketing authorisation	Strength	Pharmaceutical form	Route of administration	Marketing status

Centre-indications (SmPC)	Warnings and precautions (SmPC)	Undesirable effects (SmPC)	Contra-indications (PIL)	Warnings and precautions (PIL)	Undesirable effects (PIL)	Main differences between the SmPC/PIL in the different EU Member States

b)

INNs	Product name	Country	Sales figures	Estimated patient exposure (in number of treatment per year)	Estimated target population (women between 18 and 49 years in the post-auturn)