NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France - ANSM

Product Name(s) in the Referring Member State, if applicable Strength(s) and Pharmaceutical Form(s)	All medicinal products containing substances related to valproate All pharmaceutical forms, strengths and routes of administration.
Applicant(s)/Marketing Authorisation Holder(s) in the referring Member State	Sanofi-Aventis and all other MAHs

In October 2014, following an Article 31 referral (EMEA/H/A-31/1387) that reviewed all available data on the safety and efficacy in female children, women of childbearing potential and pregnant women treated with valproate and related substances, the PRAC recommended restrictions to the use of valproate and related substances containing medicinal products in the above mentioned populations and in all authorised indications, due to the risk of neurodevelopmental disorders and congenital abnormalities. The product information (PI) for all valproate containing products was updated accordingly. Moreover, educational materials were provided in the EU to all healthcare professionals and targeted patients. These included a guide for prescribers, a patient booklet, an acknowledgment of risk information form, and a DHPC.
The PRAC also recommended a drug utilisation study (DUS) to be conducted in order to assess the effectiveness of the above risk minimisation measures (RMMs).

In France, all the RMMs recommended by the PRAC have been implemented. Besides, additional measures were taken by France, such as a warning on the outer packaging, and additional DHPCs circulated; recommendations on how to replace valproate in female children, women of childbearing potential and pregnant women treated for epilepsy or bipolar disorder were also published by French authorities [HAS (the French HTA) and ANSM].

More recently, other RMMs have been implemented at national level (a patient alert card and a pictogram on the outer packaging).

A national pharmacoepidemiological study programme covering all the indications of valproate products (based on data of French national medico-administrative databases) was set up in addition to the European Union-level post-authorisation safety study requested by the PRAC, together with a national survey conducted in a sample of pharmacies in April-June 2016.

The results of these studies:

1. Provide evidence of a persistently high level of exposure to sodium divalproate and valpromide (bipolar disorder indication only) among women of childbearing potential in the recent period in France. Indeed, 27,707 women aged 15-49 years had at least one reimbursement for these products during the first trimester 2016;

Sodium divalproate and valpromide are the only valproate related substances authorised in France for the treatment of manic episodes of bipolar disorder in case of contraindication or lithium intolerance.

2. Show that among pregnant women, sodium divalproate and valpromide are generally stopped early during the course of pregnancy, i.e. during the first trimester: among women ever exposed during their pregnancy between 2007 and 2014, 94% had been exposed during the first trimester versus 15% during the second and 14% during the third trimester. This situation contrasts with that of valproic acid prescribed for epilepsy, for which exposure is largely maintained throughout pregnancy (85%, 68% and 66% exposed during the first, second and third trimester, respectively), suggesting that therapeutic alternatives may be more easily considered in patients with bipolar disorders ;

3. Show that prescribing conditions are poorly respected, especially in psychiatry: a study conducted in a national sample of 222 pharmacies showed that in April-June 2016, conditions regarding supply and use were respected in only 36% of dispensing among girls and WCBP who had been prescribed valproic acid by a psychiatrist.

Psychiatrists, consulted by the ANSM on this concern, were favourable to contraindicate valproate containing products during pregnancy and in women of childbearing potential without effective contraception in the treatment of manic episodes of bipolar disorder, since other therapeutic alternatives are available, both non pharmacological and pharmacological treatments.

Furthermore :
- the above mentioned study conducted in a national sample of 222 pharmacies, showed that prescribing conditions were respected in only 50 % of dispensing among girls and WCBP who had been prescribed valproic acid by a neurologist ;
- data sourced from UK (prescribing data (Jan-June 2016) using the CPRD and patient survey data (April 2016)) has established the lack of effectiveness of the risk minimisation measures taken to date, including that healthcare professionals and patients are still not sufficiently aware of the risks (despite repeated communication) or that they are aware of the communications but are unclear how the new information should impact their prescribing decisions. This has been observed for all valproate indications.

In view of the above, the ANSM considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether:

1. there is a need to contra-indicate valproate and related substances during pregnancy and in women of childbearing potential with no effective contraception in the treatment of manic episodes of bipolar disorder;

2. in light of a review of the effectiveness of the current risk minimisation measures across all indications, additional risk minimisation measures should be considered for valproate containing products and whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed:

Date: / 8 MARS 2017

Dr Dominique MARTIN

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Directeur général