09 March 2017
EMA/PRAC/154222/2017

PRAC List of questions

To be addressed by the marketing authorisation holder(s) of medicinal products containing substances related to valproate

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1454

Active substance: sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium

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The marketing authorisation holders MAH(s) are requested to address the following questions:

Question 1

The MAHs should provide any new data since the finalisation of the Article 31 referral under 2001/83/EC in 2014 on the benefit/risk profile of valproate and related substances (hereinafter 'valproate') in all authorised indications in the treatment of Women of Child Bearing Potential (WCBP) and pregnant women. Based on European or international recommendations, the therapeutic value of valproate among the currently available therapeutic options for all authorised indications should be discussed. The discussion should include the therapeutic value of valproate for the treatment of WCBP in view of other available therapeutic alternatives for each indication, and the known risks of valproate in pregnancy.

Question 2

The MAHs should provide available evidence of treatments in patients who only respond to valproate. The MAH should indicate the proportion of patients who may respond only to valproate for each of the authorised indications. Any data on the risk of relapse if the treatment has been discontinued in such patients should be also provided. This should include information on the time to relapse after discontinuation of valproate and if the discontinuation is abrupt or gradual.

Question 3

The MAHs should discuss the specific reasons for continuing the treatment in female patients, in particular in WCBP who become pregnant, as well as the initiation of treatment with valproate in pregnant women and in WCBP, taking into account the risks of valproate in pregnancy. The MAHs should also detail and discuss any alternative treatment in these specific populations in all authorised indications.

Question 4

The MAHs should provide all data on the qualitative and quantitative use of valproate in the treatment of female patients/WCBP and compare the data in the period before and after all risks minimisation measures implemented following the conclusion of the previous referral. This comparison should include:

- Prescription rates of valproate in WCBP (with a stratification of patients that received valproate as monotherapy), stratified by indication;
- Pregnancy rates among WCBP who are using valproate, stratified by indication;
- Change in rates of valproate discontinuation among WCBP with a stratification of patients in whom valproate was discontinued due to pregnancy and the timing of the discontinuation (i.e. 1st, 2nd, 3rd pregnancy trimester), stratified by indication.

In addition, where available, the data should be presented per country.

Question 5

The MAHs should provide all available information on measures taken and analyses / studies that have been done to evaluate the effectiveness and awareness (of both healthcare professionals and patients) of the risk minimisation measures (RMMs) implemented after the 2014 referral and provide results of these measures/analyses /studies.
The MAHs should provide details of additional measures that have been implemented at national level in addition to the ones resulting from the referral in 2014 in order to minimise the risks related to

exposures in pregnancy and comment on the impact of such measures and the use of valproate in WCBP and pregnant women.

Question 6

The MAHs should discuss any other proposals (in addition to the ones agreed after the previous 2014 referral) for measures to further minimise the risks of valproate exposure in pregnancy and exposure in WCBP and possibilities for further RMMs e.g. the need for contraindications during pregnancy in WCBP without effective contraception, a pregnancy prevention programme (PPP) and any other measure that might be useful.