10 October 2013
EMA/PRAC/611881/2013

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for substances related to valproate

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

Procedure number: EMEA/H/A-31/1387

INN: sodium valproate, valproic acid, valproate semisodium, valpromide

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The marketing authorisation holders MAH(s) for medicinal products containing valproate related substances are requested to provide the following:

Question 1

The MAHs should provide information on the following:

a) 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.

b) The posology, treatment duration, contraindications, warnings and precautions and undesirable effects included in the summary of products characteristics (SmPC) and the package leaflet (PL) 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.

c) 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 relating to valproate use during pregnancy 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 the use of their product in pregnant women, women planning pregnancy and women of childbearing potential for all licensed indications. Based on European or international recommendations, the place of valproate in the treatment of the above populations among the currently available therapeutic armamentarium for the authorised indications should be discussed.

Question 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.

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

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

TABULATION

a)

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

Contra-indications (SmPC)	Warnings and precautions (SmPC)	Undesirable effects (SmPC)	Contra-indications (PL)	Warnings and precautions (PL)	Undesirable effects (PL)	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 15 and 49 years, in the post-partum)