01 September 2022
EMA/PRAC/702490/2022

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for topiramate-containing medicinal products

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

Procedure number: EMEA/H/A-31/1520

INN/active substance: topiramate

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Questions

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

Question 1

Concerning your topiramate-containing medicinal product(s), please complete the annexed tables with:

a) Information on authorised indication(s). Figures on exposure of pregnant women, women of childbearing potential (above 18 years of age) and of girls/female adolescents (below 18 years of age). This should be stratified by Member State in the EU[1], by authorised indication/any use in non-authorised indication and per year.

b) Contraindications (section 4.3), warnings and precautions (section 4.4), fertility, pregnancy and lactation (section 4.6) and undesirable effects (section 4.8) included in the summary of products characteristics (SmPC), and corresponding text from 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.

c) Overview of additional risk minimisation measures, as applicable.

d) Information on the legal status.

Question 2

Please provide a cumulative literature review of studies addressing neurodevelopmental outcomes in children exposed to topiramate during pregnancy. Based on this review, a critical assessment of the available literature should be included, with a particular focus on the recently published study by *Bjørk et al*[2].

A discussion on causality with respect to increased risk for neurodevelopmental outcomes following exposure to topiramate during pregnancy should be submitted. This should take any relevant information regarding potential mechanism(s) as well as relationship with dose into account. Furthermore, the magnitude of the risk, including the absolute risk, should be commented on, as applicable.

Question 3

Please provide an assessment of the benefit-risk balance of the use of your medicinal product(s) in pregnant women, women planning pregnancy and women of childbearing potential, as well as in girls/female adolescents (below 18 years of age) taking into account relevant information including clinical guidelines. The following should be addressed:

a) Treatment of epilepsy should be discussed in depth, including whether there are sub-populations with specific types of seizures that can only be adequately treated with topiramate.

b) Treatment of migraine as well as body weight management should also be discussed while acknowledging that these populations are already contraindicated for such uses.

[1] EU should be understood as including EU, Norway and Iceland
[2] Bjørk M, Zoega H, Leinonen MK, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

Question 4

Please comment on whether the current measures in place are sufficient to minimise risk for serious birth outcomes including neurodevelopmental disorders after exposure to topiramate during pregnancy. If not, provide proposals and justifications for further measures, including changes to the product information (SmPC and PL) and additional risk minimisation measures, to minimise the risk of serious birth outcomes including neurodevelopmental disorders due to exposure to topiramate during pregnancy. This should include:

a) A discussion on updates of the product information to reflect current knowledge about the risk for neurodevelopmental disorders following exposure to topiramate during pregnancy, including the magnitude of the risk and the most frequently observed neurodevelopmental disorders. This should also include a discussion of the need for a visual reminder on the outer packaging.

b) A discussion on the need for additional risk minimisation measures for healthcare professionals and patients, including measures to ensure that women are adequately informed about the risks for serious birth outcomes including neurodevelopmental disorders due to exposure to topiramate during pregnancy. Please refer to current guidance published on the EMA website for further details on possible tools.

Question 5

Please provide a proposal for activities to assess the effectiveness of risk minimisation measures to be implemented. This should include a proposal for a drug utilisation study to monitor the effectiveness of the measures to minimise the risk for serious birth outcomes including neurodevelopmental disorders.

Annex

Question 1

a)

INN	Product name	Member State	Authorised indication(s)	Estimated patient exposure[1]	Year

[1]. Expressed in patient years and stratified by Member State, by authorised indication: i) for pregnant women, ii) for women of childbearing potential (above 18 years of age) and iii) for girls/female adolescents (below 18 years of age). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided. For any use outside authorised indication(s), MAH should replicate this table, replace the 'authorised indication' column by 'use outside authorised indication(s)' and provide figures accordingly.

b)

Product Information	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Per indication[2]			
Contraindications			
Warnings and precautions			
Fertility, pregnancy and lactation			
Undesirable effects			

[2]. MAH should clearly indicate the authorised indication in the cell and replicate the table for each authorised indication.

c)

Additional risk minimisation measure(s)	Per indication	Member State

d)

Legal status of your medicinal product(s)[3]	**Prescription only (POM): Yes /No**	**Restricted prescription[4]: Yes /No**	**Over the counter (OTC): Yes /No**
Information on restricted prescription[5]			
INN	**Product name**	**Restricted prescription details:**	**Member State**
Information on OTC [6]			
INN	**Product name**	**Authorised indication**	**Member State**

[3]. MAH should indicate if their medicinal product(s) hold(s) a POM status, restricted prescription status, and/or OTC status.
[4]. Restricted prescription to healthcare professional (HCP) specialists or other type(s) of restriction(s).
[5]. MAH should only further complete this table section for medicinal product(s) with a restricted prescription or other restricted status type(s).
[6]. MAH should only further complete this table section for medicinal product(s) with an OTC status.