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 Names in the Referring Member State:	Epitomax and generics
Active substance	Topiramate
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s) in the referring Member State	Various

Background

Topiramate is an antiepileptic drug (AED) and was first approved on 18 July 1995 in the United Kingdom. In the EU, topiramate is indicated in seizures (partial seizures; adjunctive therapy in partial onset seizures; generalised tonic clonic seizures; seizures associated with Lennox-Gastaut syndrome) and in the prophylaxis of migraine. Topiramate is also authorised in some EU Member States as a fixed dose combination with phentermine for weight management in adult patients.

It has been established that topiramate is teratogenic in mice, rats and rabbits. In humans, topiramate crosses the placenta and similar concentrations have been found in the umbilical cord and maternal blood. Clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have a 3-fold increased risk of congenital malformations, including cleft lip and palate, hypospadias and microcephaly. The risk of congenital malformations is currently addressed in the EU product information but to date, a risk of neurodevelopmental disorders has not been identified.

In the prophylaxis of migraine indication and weight management (in fixed dose combination with phentermine), topiramate is contraindicated during pregnancy and in women of childbearing potential who are not using effective methods of contraception, whilst highly effective contraception is recommended to be used in women of childbearing potential treated for seizures.

Issues to be considered

Results of a pharmacoepidemiological study by Bjørk *et al* [1] on neurodevelopmental disorders associated with *in utero* exposure to several AEDs (ten most frequently used as monotherapies and five dual therapies), including valproate and topiramate were recently published. This study is based on several Nordic registries from Sweden, Norway, Finland, Denmark, and Iceland. Data concerning prenatal exposure to AEDs were collected between 1996 and 2017 and represented a total of almost 4.5 million mother-child pairs including 24,825 children exposed *in utero* to at least one AED and followed on average until their 8th year.

The authors found that prenatal exposure to topiramate, valproate, and several duotherapies were associated with increased risks of neurodevelopmental disorders.

In the study by Bjørk *et al.*, results with topiramate as monotherapy were as follows:

1. an increased risk of autism spectrum disorder, ASD (aHR* = 2.77; CI 95% [1.35; 5.65]) in children whose mothers with epilepsy were exposed to topiramate monotherapy during pregnancy (on a total number of children, n=246), compared with children whose mothers with epilepsy were not exposed to AED (n=21,634).

2. an increased risk of intellectual disability, ID (aHR* = 3.47; CI 95% [1.40; 8.63]) in children whose mothers with epilepsy were exposed to topiramate monotherapy during pregnancy (n=246), compared with children whose mothers with epilepsy were not exposed to AED (n=21,634).

Significant increased risks of ASD and ID were also observed in children with prenatal exposure to topiramate when compared to children from the general population, and regardless of the dosage strength. These results suggest that the risk of neurodevelopmental disorders would concern all indications of topiramate containing products.

A 3- to 5-fold increased risk of ASD and ID in children after prenatal exposure to valproate has been demonstrated through several studies. This study confirms the known risk of neurodevelopmental disorder associated to valproate. The data collected in this study predates the implementation of risk minimisation measures for valproate in this respect, (measures were last strengthened further to a referral procedure concluded in 2018 (EMEA/H/A-31/1454)), therefore no further actions are considered warranted for valproate based on those results.

Some duotherapies were associated with increased risks of neurodevelopmental disorders in children of women with epilepsy. For these duotherapies, groups were small and outcomes few, which increase the uncertainty with these findings. It is expected that duotherapies are used in more severe and/or therapy-resistant forms of epilepsy and these results support the presence of confounding by indication. Based on these observations, these duotherapies do not raise concerns of the same magnitude as those with topiramate.

In view of those results, France initiated in June 2022 a signal procedure at the European level in order to evaluate the risk of neurodevelopmental disorders due to *in utero* exposure to topiramate.

In parallel, also taking into account the number of women exposed to topiramate in France (301 pregnant women and 32,403 women of childbearing potential in 2021, source: Système national des données de santé (SNDS) - French National Health Data System), the ANSM, while awaiting further assessment at the European level, initiated actions at national level to further

enhance risk minimisation measures of topiramate-containing products. Further to a national stakeholders'consultation, the ANSM is considering the implementation of a risk acknowledgement form, an annual prescription by a neurologist or a paediatrician for women of childbearing potential, pregnant women, and female children/adolescents, respectively.

In July 2022, PRAC considered that the study by Bjørk *et al* - despite limitations - raised further concerns to the established risks with exposure to topiramate during pregnancy and that a thorough assessment of the potential risk for neurodevelopmental disorders was warranted, including ASD and ID due to *in utero* exposure to topiramate.

Given the increased risk of neurodevelopmental disorders highlighted by this study with *in utero* exposure to topiramate and the known risk of congenital malformations, an in-depth review of all the available data about the benefit-risk of topiramate in pregnant women/women of childbearing potential in all therapeutic indications should be carried out in order to discuss in particular, the effectiveness of current risk minimisation measures and the need to implement additional risk minimisation measures (including a pregnancy prevention programme).

In view of the above and the necessity to take an action at EU level, France, 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 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 PRAC.

Signed [redacted]

Date

22 AOUT 2022

1- 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)

**aHR. Hazard ratio (95% CI), adjusted for maternal age, education and marital status, parity, child's birth year, sex, and country of birth, maternal use of antidepressants or opioids, depression, anxiety, personality disorders, number of chronic somatic diseases, and number of hospitalisations the year before last menstrual period.*