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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Topiramate-containing medicinal products

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AED	Antiepileptic drug
ADHD	Attention deficit hyperactivity disorder
aHR	Adjusted hazard ratio
AMPA	Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ASD	Autism spectrum disorder
ASM	Anti-seizure medication
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BW	Birth weight
CI	Confidence interval
DHPC	Direct healthcare professional communication
DLP	Data lock point
EEA	European Economic Area
EPITT	European pharmacovigilance issues tracking tool
EU	European Union
EUROCAT	Epidemiological surveillance of congenital anomalies
GA	Gestational age
GABA	Gamma-aminobutyric acid
HR	Hazard ratio
ICD	International classification of diseases
ICSR	Individual case safety reports
ID	Intellectual disability
IQR	Interquartile range
MAH	Marketing authorisation holder
MCM	Major congenital malformation
NDD	Neurodevelopmental disorder
NICE	National Institute for Health and Care Excellence
PSUR	Periodic safety update report
PSUSA	PSUR single assessment

RMP	Risk management plan
RR	Relative risk
SAG-N	Scientific Advisory Group on Neurology
SD	Standard deviation
SGA	Small for gestational age
SSRI	Selective serotonin reuptake inhibitor
WCP	Women of childbearing potential
WWE	Women with epilepsy
WWOE	Women without epilepsy

1. Information on the procedure

In 2022, a pharmacoepidemiological study by Bjørk et al., 2022 was published in the literature on neurodevelopmental disorders (NDDs) associated with in utero exposure to several antiepileptic drugs (AEDs) based on data from Nordic registries collected between 1996 and 2017. The study included 4.5 million mother-child pairs including nearly 25,000 children exposed in utero to at least one AED and followed-up until their eighth year of life on average. The study results suggest an increased risk of autism spectrum disorders (ASDs) and intellectual disability (ID) in children whose mothers were taking topiramate during pregnancy.

Based on this publication, a signal procedure was initiated at PRAC in July 2022 to review these new data and consider regulatory implications as applicable.

On 22 August 2022, France (ANSM) triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns taking into account the known risk of congenital malformations on the benefit-risk balance of topiramate-containing products in pregnant women and women of childbearing potential (WCP) in all therapeutic indications and to issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Topiramate belongs to the pharmacotherapeutic group of 'antiepileptics' (ATC classification system code: N03AX11). Topiramate is an AED that blocks voltage-gated sodium channels, reduces membrane depolarisation through-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtypes of glutamate receptors, enhances gamma-aminobutyric acid (GABA)(A) receptor activity. It is also a weak inhibitor of carbonic anhydrase, but the precise mechanism of action is unknown.

Topiramate was first approved in July 1995 in the United Kingdom. Medicinal products containing topiramate as a monocomponent are currently authorised in all European Union (EU)/European Economic Area (EEA) Member States. Topiramate monocomponent is indicated in the treatment of seizures and as prophylaxis of migraine.

In June 2021, a fixed dose combination product containing topiramate/phentermine was authorised via a decentralised procedure (SE/H/1963/001-004/DC) in Denmark, Finland, Iceland, Norway, Poland and Sweden for the treatment of obesity and overweight under certain conditions.

It is well-established that topiramate is teratogenic in mice, rats, rabbits and humans. In humans, topiramate crosses the placenta and similar concentrations have been found in the umbilical cord and maternal blood. It is further known that 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, which is already reflected in the product information.

The current product information for topiramate monocomponent products contains information about these risks and a number of measures to reduce exposure of pregnant women are described. For the topiramate/phentermine combination product, in addition to the product information, there is an educational material for healthcare professionals as well as for patients, which includes the risk for serious adverse birth outcomes after in utero exposure to topiramate, and the measures for risk

minimisation. Furthermore, a drug utilisation study to address the effectiveness of the risk minimisation measures to avoid use in pregnancy is in place.

According to the latest periodic safety update report (PSUR) single assessment (PSUSA) procedure for topiramate (PSUSA/00002996/202201) finalised in September 2022, the cumulative worldwide exposure (1995-2022) was 14,6 million person-years, and around 27% occurred in the EU. During the PSUR period (2017-2022), the exposure in the EU was approximately 835,000 person-years. The first PSUSA for topiramate/phentermine fixed dose combination (PSUSA/00010956/202207) was finalised in February 2023. The cumulative exposure since authorisation in 2012 in the USA was approximately 126 million capsules.

Based on the results of the study by Bjørk et al., 2022, France initiated in June 2022 a signal procedure at the European level (EPITT No. 19825) to evaluate the risks of in utero exposure to topiramate. Following initial evaluation at the PRAC, a thorough assessment of the potential risk of neurodevelopmental disorders was considered warranted, and resulted in the initiation of the current referral procedure under Article 31 of Direction 2001/83/EC.

The PRAC considered all available data in relation to the potential risk of NDDs taking also into account any new evidence on the known risks of congenital malformations and foetal growth restriction based essentially on data from the literature. A summary of the most relevant information is included below.

2.2. Efficacy aspects and therapeutic context

Treatment of epilepsy

Epilepsy is a disease characterised by recurrent seizures, which can be of different types. It is one of the most common chronic neurological disorders affecting WCP and may require continuous treatment during pregnancy.

Topiramate has proven its efficacy in the management of epilepsy in several randomised controlled clinical trials and is recommended in most major clinical guidelines. Given the long clinical experience and extensive use of topiramate, its benefits in the treatment of epilepsy are considered as well-known and well-established.

In the recent National Institute for Health and Care Excellence (NICE) guideline for epilepsies dated 2022, topiramate is mainly considered as an add-on, second-line, third-line or optional treatment depending on the epilepsy sub-type. Nevertheless, topiramate is considered useful in clinical practice for individual patients and continues to be part of the armamentarium of antiseizure medications (ASMs).

The currently approved indications in epilepsy read as follows:

- Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised tonic-clonic seizures and primary generalised tonic-clonic seizures,
- Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.

For an individual patient, recommendation for a specific anti-epileptic drug should always be based on individual factors. It is not uncommon that different options are tried in patients before adequate seizure control is reached.

There are no new efficacy data questioning the benefit of topiramate in the management of epilepsy in line with its approved indications.

Prophylaxis of migraine

Migraine is a common neurological disorder characterised by recurrent headaches that are generally associated with nausea and/or light and sound sensitivity. Prophylactic therapy decreases the frequency, severity, and duration of migraine attacks. It also increases responsiveness to acute migraine therapy and improve the quality of life.

Topiramate has proven its efficacy in the prophylactic treatment of episodic migraine randomised controlled clinical trials and is recommended in several guidelines often as a second-line choice. This in line with the currently approved indication reading as follows:

- In adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options.

However, migraine is not a life-threatening disease and there is a possibility to discontinue treatment relatively rapidly without serious medical consequences to patients and foetuses as applicable, in line with the dose reduction recommendations of the current product information. For preventive treatment of episodic migraine in pregnant women, various alternative options are available.

There are no new efficacy data questioning the benefit of topiramate in the prophylaxis of migraine in line with its approved indications.

Treatment of overweight

Over the years, the prevalence of overweight and obesity has increased amongst WCP and pregnant women.

The development programme for the topiramate/phentermine fixed dose combination product included four pivotal phase 3 studies, which overall supported a clinically relevant weight reduction under certain conditions, and which were the basis for granting the marketing authorisation(s) in Denmark, Finland, Iceland, Norway, Poland and Sweden. The approved indication reads as follows:

- Adjunct to reduced calorie diet and physical activity for obese patients (BMI ≥ 30 kg/m^2), or overweight patients (BMI ≥ 27 kg/ m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia.

There are no new efficacy data questioning the benefit of topiramate in the treatment of obesity or overweight in line with its approved indications.

2.3. Safety aspects

2.3.1. Neurodevelopmental disorders

Based on a search conducted in EudraVigilance and reviews submitted by the marketing authorisation holders (MAHs), a very limited number of individual case safety reports (ICSR) on NDDs was retrieved. The available data did not allow to conduct signal detection analyses that could be meaningful in terms of causality assessment. In addition, there were no new safety data from clinical trials available on these outcomes. A number of literature articles were reviewed in the framework of the present procedure. The following epidemiological studies were considered most relevant for the assessment of NDDs in children born to mothers exposed to topiramate during pregnancy and are further detailed below.

Bjørk MH et al., 2022

The study by Bjørk et al., 2022 is a Nordic register-based study of anti-epileptic drug in pregnancy (SCAN-AED) aiming at filling knowledge gaps concerning prenatal exposure to ASMs (10 most frequently used monotherapies and 5 dual therapies) and NDDs. The objective of this large population-based cohort study was to determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have an increased risk of NDDs. All live-born infants in Denmark (1997-2017), Finland (1996-2016), Iceland (2004-2017), Norway (2005-2017) and Sweden (2006-2017) were included in the study. Mother-child pairs, pregnancy characteristics, prescription fills, mother and child diagnoses, demographic and socioeconomic information from the national health and social registers in each country were identified. The definition of prenatal exposure was the mother filling at least 1 ASM prescription from her last menstrual period until birth.

The diagnoses of ASDs, ID or any NDDs at age of 8 years in exposed and unexposed children was determined by child psychiatrists and psychologists in specialist healthcare, according to the International Classification of Diseases, tenth revision (ICD-10) diagnostic codes. For these different diagnoses, children were considered to have ASDs if they had at least one occurrence of a diagnosis of childhood autism (F84.0), atypical autism (F84.1), and Asperger syndrome (F84.5), and children with ID if they had at least one occurrence of a diagnosis of mild ID (F70), moderate ID (F71), severe ID (F72), and profound ID (F73). The diagnoses were not mutually exclusive. NDDs were defined as a composite neurodevelopmental outcome including any NDD, as any of the diagnoses above, plus other childhood disintegrative disorder (F84.3), disorder of mental retardation and stereotyped movements (F84.4), other pervasive developmental disorder (F84.8), unspecified pervasive developmental disorder (F84.9), or unspecified ID (F79).

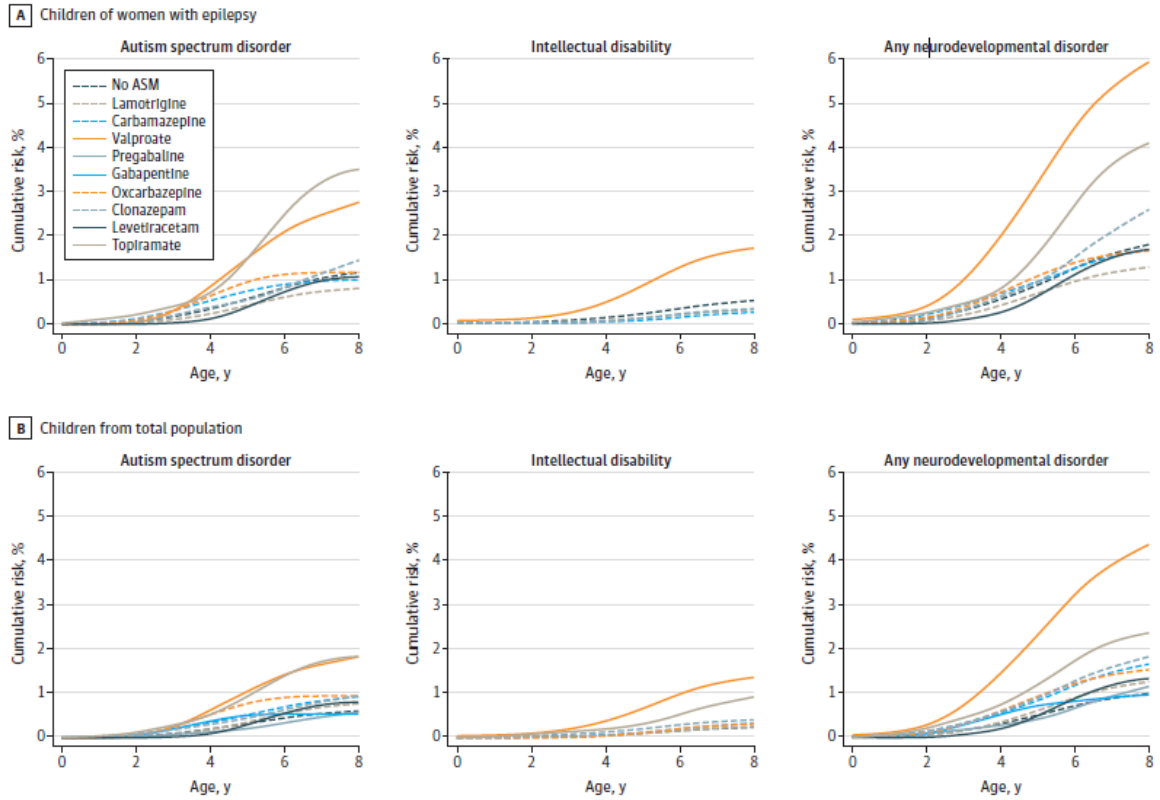
Child's sex, birth year and maternal characteristics (birth country, age, parity, marital status, education, concurrent antidepressant and opioid use, depression, anxiety, personality disorders, number of somatic diagnoses, and hospitalisations in the year preceding pregnancy) were included as covariates in all analyses. Measurements of potential confounders such as disease severity (numbers and type of seizures during pregnancy), serum concentrations of AEDs, alcohol consumption, periconceptional folate use, father's education, family history (when investigating ASD) were not available.

Of the 4,463,879 pregnancies followed in this study, 24,825 (0.6%) were prenatally exposed to AEDs of whom 16,170 were born to mothers with epilepsy. Children's mean age at diagnosis was between 6.1 and 7.9 years across all countries. The median (interquartile range (IQR)) age at the end of follow-up was 8 (4.0-12.1) years.

The number of children exposed to topiramate through their mothers during pregnancy in the total population was 471. The number of events was low namely 12 children with ASDs and 6 children with ID. In women with epilepsy, there were 246 exposed children for whom the number of outcomes was not presented due to personal data protection rules because of the low number (<5). The estimated risk of these events was increased after prenatal exposure to topiramate compared with children of women with epilepsy who did not receive ASM, as well as compared with the general population after adjustment for maternal factors. However, the precision of these estimates was low due to the low number of events.

Cumulative incidence data of NDD showed that children's mean age at diagnosis was between 6.1 and 7.9 years across all countries for the various AEDs compared to no ASM. See figure 1 below.

Figure 1. Cumulative incidence of NDDs, after prenatal exposure to ASM



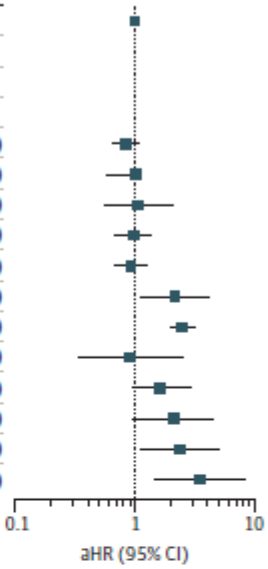
For the majority of monotherapies, higher risk estimates were observed in the general population than in the sub-population restricted to maternal epilepsy. Only topiramate risk estimates were similar in both populations. The risk estimates observed in the general population are likely overestimated due to confounding, as maternal epilepsy is positively associated with NDDs in children, and women with epilepsy are more likely to be treated with ASMs than women without epilepsy. Therefore, analyses restricted to maternal epilepsy were of primary interest for risk assessment of ASDs and ID in topiramate-exposed children.

In the population of children of women with epilepsy, 16,170 (42.8%) children were prenatally exposed and 21,634 (57.2%) were unexposed to ASMs. Among the unexposed children, 1.5% had a diagnosis of ASD and 0.8% had a diagnosis of ID by the age of 8 years. In same-aged children of mothers with epilepsy exposed to topiramate and valproate monotherapy, 4.3% and 2.7% had ASD, respectively, and 3.1% and 2.4% had ID. As the absolute number of cases exposed to topiramate was low for both outcomes ASD and ID, observed risk estimates showed a low precision. The full adjusted hazard ratios (aHRs) for ASD and ID were 2.77 (95%CI 1.35-5.65) and 3.47 (95%CI 1.40-8.63), respectively. Even for the combined outcome any NDD, only 10 events were observed resulting in an aHR of 2.13 with a rather low precision (95% CI 1.13-4.01). See figure 2 below.

Figure 2. Association between prenatal ASM exposure and child with NDD

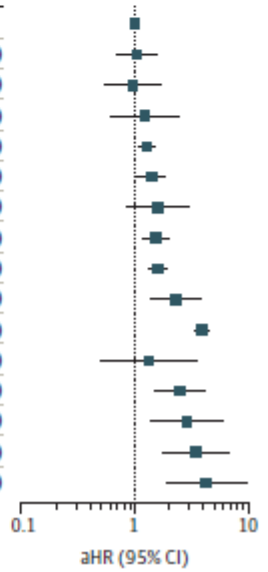
A Children of women with epilepsy

Exposure	8-y incidence, %	No. with ND	aHR (95% CI)
Unexposed, n = 21 634	2.4	443	1 [Reference]
Pregabalin, n = 91	NA	<5	NA
Gabapentin, n = 110	NA	<5	NA
Phenobarbital, n = 45	NA	<5	NA
Lamotrigine, n = 5073	1.8	81	0.83 (0.65-1.06)
Clonazepam, n = 318	4.5	15	1.00 (0.58-1.04)
Levetiracetam, n = 1004	2.1	10	1.06 (0.56-2.02)
Oxcarbazepine, n = 1429	2.0	[a]	0.97 (0.68-1.37)
Carbamazepine, n = 2609	1.9	65	0.92 (0.68-1.25)
Topiramate, n = 246	5.1	10	2.13 (1.13-4.01)
Valproate, n = 1884	6.5	152	2.44 (1.94-3.07)
Lamotrigine + levetiracetam, n = [a]	1.6	[a]	0.91 (0.34-2.48)
Valproate + lamotrigine, n = 312	5.5	[a]	1.65 (0.95-2.85)
Lamotrigine + oxcarbazepine, n = [a]	4.3	[a]	2.07 (0.96-4.49)
Lamotrigine + topiramate, n = 123	7.5	[a]	2.35 (1.13-4.87)
Levetiracetam + carbamazepine, n = [a]	5.7	[a]	3.46 (1.46-8.18)



B Total cohort

Exposure	8-y incidence, %	No. with ND	aHR (95% CI)
Unexposed, n = 4 463 879	1.3	68 295	1 [Reference]
Pregabalin, n = 1666	2.9	25	1.05 (0.71-1.55)
Gabapentin, n = 965	2.4	12	0.96 (0.54-1.69)
Phenobarbital, n = 175	2.6	8	1.23 (0.61-2.46)
Lamotrigine, n = 7950	2.4	133	1.27 (1.07-1.50)
Clonazepam, n = 1182	3.9	48	1.40 (1.06-1.86)
Levetiracetam, n = 1017	2.1	10	1.58 (0.85-2.94)
Oxcarbazepine, n = 1539	2.0	48	1.53 (1.15-2.02)
Carbamazepine, n = 3256	2.0	99	1.59 (1.30-1.93)
Topiramate, n = 471	4.0	16	2.29 (1.40-3.74)
Valproate, n = 2421	5.9	190	3.87 (3.36-4.47)
Lamotrigine + levetiracetam, n = 414	1.6	<5	1.32 (0.50-3.52)
Valproate + lamotrigine, n = 363	5.3	15	2.50 (1.51-4.15)
Lamotrigine + oxcarbazepine, n = 130	4.2	7	2.86 (1.36-6.01)
Lamotrigine + topiramate, n = 148	7.8	9	3.45 (1.79-6.63)
Levetiracetam + carbamazepine, n = 136	5.7	6	4.26 (1.91-9.50)



Several sensitivity analyses were performed to check the robustness of the applied method. However, these analyses were performed in the general population for the combined outcome only. One example was to estimate the results if the women had discontinued treatment before pregnancy. See table 1 below.

Table 1. Risk of any NDD in children prenatally exposed to ASM in monotherapy using women discontinuing ASM before pregnancy as a reference.

	N Exposed	N ND	Adjusted hazard ratio (95% confidence interval)[d]
Children of valproate discontinuers	1239	39	1
Valproate exposed children	1468	92	2.01 (1.32-3.04)
Children of carbamazepine discontinuers	1108	31	1
Carbamazepine exposed children	2051	64	1.41 (0.88-2.26)
Children of lamotrigine discontinuers	4377	83	1
Lamotrigine exposed children	8489	142	0.79 (0.60-1.05)
Children of pregabalin discontinuers	3195	51	1
Pregabalin exposed children	2064	33	0.86 (0.54-1.38)
Children of gabapentin discontinuers	3402	57	1
Gabapentin exposed children	1658	19	0.54 (0.30-0.98)
Children of oxcarbazepine discontinuers	257	10	1
Oxcarbazepine exposed children	582	28	1.78 (0.79-4.00)
Children of topiramate discontinuers	1095	15	1
Topiramate exposed children	679	22	2.29 (1.09-4.82)
Children of clonazepam discontinuers	870	41	1
Clonazepam exposed children	808	37	0.87 (0.54-1.42)

Regarding dose relationship, the authors found that the aHR was 1.7 (95% CI, 1.0-2.8) for any NDD associated with topiramate doses less than 100 mg per day and 2.9 (95% CI, 1.3-6.7) for doses 100 mg per day or more compared with children from the general population. For valproate, the aHR was 2.3 (95% CI, 1.9-2.8) with doses less than 750 mg per day and 5.6 (95% CI, 4.7-6.8) with doses of 750 mg or more per day. For the other AEDs, minimal or no dose-related associations were observed.

Discussion

The study of Bjørk et al., 2022 presents several strengths. First, the study is based on well-established national population-based healthcare registers from countries with similar healthcare context and health data structure. Second, the outcome specificity was increased by measuring two diagnoses (ASD and ID) or any NDD. Third, the follow-up of children occurred at a relatively high age (median of 8 years) which increases the sensitivity of outcome detection.

The identification of a subpopulation with epilepsy was also central to the interpretation of the results and was based on any occurrence of a relevant discharge diagnosis code for epilepsy. Since there is a fixed start date for access to data in the respective registers, it means that the look-back period is longer for pregnancies in the later part of the study period. Therefore, the sensitivity of the definition

increases with time. This may contribute to a time bias if there are simultaneous time trends related to ASM exposure and outcomes. However, the consequence of such bias is difficult to predict.

The classification of mothers as having epilepsy raises concerns based on the very large differences between countries. This is shown in the distribution of the overall proportion of women taking any ASM in the entire study population compared to the proportion of women with epilepsy taking any ASM. The large differences between countries, e.g. 33% of women with epilepsy in Norway and Denmark taking any ASM compared with 80% in Finland, cannot be fully explained by differences in clinical praxis. Instead, it raises concerns regarding the validity of the definitions and data used to classify epilepsy.

Adjustment for birth year and country of birth was intended in the analysis and could attenuate the concerns for a time bias. It is unclear whether the stratified Cox regression method used fully addressed the problem of time bias. Therefore, no conclusion could be drawn on this. Moreover, live births are the statistical analysis units but the analysis did not account for dependencies between siblings with the same mother.

Another potential limitation related to the data sources used concerns the outcome of ASD and ID largely expected to be diagnosed in an outpatient setting. As an example, the coverage of specialist outpatient visits in the Swedish patient register is incomplete but increased over the study period. If there is a similar change over time in the use of topiramate, this could lead to a non-negligible time bias related to calendar time. Since the extent of coverage over time and in the different data sources is not available, it was not possible to quantify the consequences of this potential bias.

Further, confounding by indication and selection bias from other mechanisms are the most important limitations to the validity of the study results. The selection of the most suitable AED treatment remains at the level of individual patient evaluation. Since topiramate has been known for a while to be teratogenic, this factor has most likely played a role when considering treatment options in WCP or pregnant women. The low proportion treated with topiramate in the very large overall study population confirms that this group is highly selected based on patient and disease-related characteristics. If these are associated with the risk for neurodevelopmental outcomes, this introduces confounding. It also illustrates that risk estimates are based on very few events and are therefore imprecise despite the large source population and long study period.

Of note, increased risks were also associated with all duotherapies except with levetiracetam and lamotrigine, even for those combinations where the respective individual ASM does not show any association with NDDs. Duotherapies are generally used in more severe and/or therapy-resistant forms of epilepsy. Therefore, such results for duotherapies provide further support to the presence of confounding by indication.

Regarding the observed dose relationship, it should be noted that prenatal exposure was defined as the mother filling at least 1 AED prescription from her last menstrual period until birth. The daily dose was calculated by dividing the cumulative sum of all defined daily doses prescribed between 90 days before last menstrual period to birth and then dividing by the number of days between in the same period. This assumes that patients took the dose they were prescribed, which may not have been the case. Therefore, it may lead to uncertainties in the calculations of the daily dose. Serum concentrations of many AEDs decline during pregnancy, frequently leading to an increased dose without a subsequent increase in prenatal exposure (Tomson et al., 2019). Taking into account the low number of events and the absence of serum concentrations, these circumstances make the interpretation of dose dependency questionable. The dose response calculation was based on 16 cases of NDDs exposed to a lower (<100mg) topiramate dose and 6 cases with a higher dose (≥100mg). Furthermore, any dose-response estimate was also likely confounded since higher doses are expected to be used in more severe/refractory forms of epilepsy. Taken together, the conclusion of dose dependency for an

association between topiramate and NDDs is questioned in this low number of patients. This was also underlined by the SAG-N that dose dependency cannot be assessed in this study due to the inherent uncertainties and limitations of the study.

Furthermore, the sensitivity analyses conducted in women who had discontinued treatment before pregnancy was also of interest for confounding measurement by indication. See table 1 above. While the hazard ration (HR) for this comparison was 2.29 (95% CI 1.09-4.82), it was not considered very informative for the following reasons:

- in the migraine indication, it is highly plausible that patients treated with topiramate are more prone to discontinue their treatment during pregnancy, compared to patients with (severe) epilepsy considering that migraine is a non-life-threatening condition,
- the strong restriction for use of topiramate in WCP and strong recommendation to switch therapy before pregnancy means that women still being exposed to topiramate during pregnancy is a highly selected subpopulation.

This further strengthened the issue of strong confounding by indication. Adjustment for measured confounders did not change the estimates notably which means that there is either no relevant confounding, or relevant confounders were not included or not adequately measured. There was also no discussion on how the covariates were selected nor any discussion on potential confounders or attempt to present a quantitative bias analysis.

Overall, the interpretation of this study shows that the estimated association between topiramate and NDD may have a clinically relevant magnitude, but it is measured with low precision as it is based on a few events only. There are also clear indications that a substantial part of this risk is related to the strong selection mechanisms behind the low proportion of pregnancy exposure to topiramate, meaning that confounding by indication likely threatens the validity of the risk estimate. It is not possible to determine how large the part of the estimated relative risk is due to topiramate and not to underlying patient/disease characteristics. An absolute risk could not be estimated/presented due to the low number of events. Based on the study data, there is however a possible causal role of topiramate in the observed development of NDDs following prenatal exposure. However, the evidence remains weak.

Dreier JW et al., 2023

The study by Dreier et al., 2023 is a prospective, population-based register study that assessed 4,546,605 singleton children born alive in Denmark, Finland, Iceland, Norway and Sweden between 1996-2017. The objective of this Nordic population-based register study was to examine the association between prenatal exposure to ASM with a spectrum of psychiatric disorders in childhood and adolescence in children of mothers with epilepsy. Prenatal exposure to ASM was defined as maternal prescription fills from 30 days before the first day of the last menstrual period until birth.

Information on psychiatric disorders was retrieved from patient registers. Children were considered to have a psychiatric or neurodevelopmental disorder if they were registered with any relevant main or secondary diagnosis from the ICD-10 F chapter.

Of the 4,546,605 children, 38,661 children of mothers with epilepsy were identified who were followed up to 22 years of age (mean [standard deviation (SD)] age 7.5 [4.6] years). For topiramate, 290 children of mothers with epilepsy were followed-up for 7.0 [3.7] years. Children of mothers with epilepsy unexposed to ASM had a 31.3 % (95% CI: 28.9%-33.6%) risk of being diagnosed with a psychiatric disorder by 18 years of age, whereas the corresponding risk was 42.1% (95% CI: 38.2%-45.5%) for valproate monotherapy exposure. Due to an insufficient follow-up, the cumulative incidence

of psychiatric disorders at the age of 18 was not provided for topiramate. However, at the age of 10, 20.4% children exposed to topiramate had a risk of being diagnosed with a psychiatric disorder compared to 13.9% of children unexposed to ASM and 27.2% of children exposed to valproate.

Children with prenatal exposure to topiramate had an increased risk of attention deficit hyperactivity disorder (ADHD) (aHR 2.38; 95 % CI: 1.40-4.06) and potentially of ID (aHR 2.23; 95% CI: 0.90-5.50) and ASD (aHR 1.93; 95% CI: 0.95-3.94).

Discussion

The study by Dreier et al., 2023 presents several strengths. It is based on large, well-established, and population-based healthcare registers from the Nordic countries. The study was essentially undertaken in the same dataset as the study by Bjørk et al., 2022 but focussed on mothers with epilepsy only, and on other outcomes mainly a spectrum of psychiatric disorders in childhood and adolescence. The authors used a broader exposure window and reported data for a narrower group of children, namely those whose mothers had epilepsy.

The number of topiramate-exposed children whose mothers had been treated with ASMs (n=290) was slightly larger than in the Bjørk et al., 2022 study (n=246) but still limited. Both studies found an increased risk of ID and ASD following prenatal exposure to topiramate, while in the study by Dreier et al. the association did not reach statistical significance. See table 2 below.

Table 2. Comparison of the results of the studies by Bjørk et al., 2022 and Dreier et al., 2023

	Cohort: Children of mothers with epilepsy exposed to topiramate	aHR of ASD (95% CI) [number of cases]	aHR of ID (95% CI) [number of cases]	aHR of ADHD (95% CI) [number of cases]
Dreier et al., 2023	n=290	1.93 (0.95-3.94) [8]	2.23 (0.90-5.50) [5]	2.38 (1.40-4.06) [16]
Bjørk et al., 2022	n=246	2.77 (1.35-5.65) [not applicable*]t	3.47 (1.40-8.63) [not applicable*]	Not investigated

*Owing to personal data protection restrictions on publishing tables where the difference between upper and lower panel of the table is less than 5.

The authors argued that this could be explained by the fact that the study by Bjørk et al., 2022 had a narrower exposure window applied, i.e. the 30 day period before the last menstrual period used by Dreier et al., 2023 was not included, and that this higher specificity of exposure classification tends to increase the HR. It can be assumed that a narrower exposure window is a better way to capture cases with an actual exposure to topiramate during pregnancy. Irrespectively, both evaluations point to an increased occurrence of these conditions in children who had been exposed to topiramate during pregnancy, compared to children born by mothers with epilepsy but not treated with an AED.

Furthermore, the average duration of follow-up was 7 years for prenatal topiramate-exposed children. Therefore, the cumulative incidence of psychiatric disorders at 18 years of age which was evaluated for some substances in this study was not reported for topiramate. The cumulative incidence of psychiatric disorders at the age of 10 years was higher for children exposed to topiramate during pregnancy than for children of women with epilepsy but not exposed to an ASM (20.4 % vs. 13.9%).

In addition, the study showed a significantly increased occurrence of ADHD for topiramate exposed children (aHR 2.38; 95% CI: 1.40-4.06) compared with mothers with epilepsy unexposed to an AED, which was not investigated by Bjørk et al., 2022. The known increased risk of ADHD for valproate is also confirmed by Dreier et al., 2023 (aHR 1.41; 95% CI: 1.10-1.81), which provides support for the sensitivity of the study. Further, increased point estimates for ASD and ID were also seen in this study.

Blotière PO et al., 2020

The study by Blotière et al., 2020 is a nationwide population-based cohort study using French national healthcare databases covering children born alive between 2011 and 2014 and prenatally exposed to AED monotherapy. The objective of the study was to assess the association between prenatal exposure to monotherapy with the AEDs most commonly used during pregnancy and the risk of various neurodevelopmental outcomes compared with lamotrigine.

Women were considered exposed during pregnancy when an AED had been dispensed between 30 days before the beginning of the pregnancy and the end of the pregnancy. Treatment duration and dose were calculated. The factors adjusted for related to the mother included sociodemographic covariates, comedications (preconception folic acid supplementation, selective serotonin reuptake inhibitors (SSRIs) during pregnancy, antipsychotics, severity of mental disorders), history of mental and behavioural disorders not related to alcohol or smoking. Alcohol intake and smoking were not directly available in the databases and proxies were calculated. Potential confounders related to the child were gender, gestational age (GA) and birth weight (BW).

The outcomes measured in the study included NDDs, defined by ICD-10 codes F70-F98, with two subcategories: pervasive developmental disorders (F84) and mental retardation (F70-F79) studied separately. The secondary outcome also included visits to speech therapists. The reference group was comprised of children prenatally exposed to lamotrigine. Children were followed until outcome, loss to follow-up, death or 31 December 2016.

The cohort comprised 9,034 children, 2,916 of which were exposed to lamotrigine, 1,627 to pregabalin, 1,246 to clonazepam, 991 to valproic acid, 621 to levetiracetam, 502 to carbamazepine, 477 to topiramate, 378 to gabapentin and 143 to oxcarbazepine. The median follow-up was 3.7 years (IQR, 2.7–4.7 years). None of these AEDs except valproic acid was associated with an increased risk of any of the four neurodevelopmental outcomes investigated. The estimated associations (HR) for topiramate exposure were as follows: NDDs: 0.8 (0.4 to 1.9), pervasive developmental disorders: 0.3 (0.0 to 4.9), mental retardation: 0.5 (0.1 to 3.3) and visits to a speech therapist: 1.2 (0.8 to 1.8).

The authors concluded that there was no increased risk of any of the studied neurodevelopmental outcomes observed with prenatal exposure to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam or carbamazepine, compared with lamotrigine.

Discussion

The study by Blotière et al., 2020 presents several strengths. One of the main strengths is its size being a large cohort of children prenatally exposed to AED monotherapy including 477 children exposed to topiramate specifically. Another strength is the reference group of pregnant women exposed to lamotrigine monotherapy used in the study.

Topiramate was not clearly associated with NDDs, pervasive developmental disorders or visits to a speech therapist. The median follow-up was 3.7 years which limits the sensitivity of the study to capture NDDs. However, valproate was associated with an increased risk for all outcomes, also with a dose-response relationship, which provides support for 'assay sensitivity' in the study.

In a supplementary to the study by Coste et al., 2020 conducted in the same population but focused on valproate, information on timing of exposure with topiramate is available. In approximately 75% of topiramate-exposed pregnancies, exposure had occurred during the first trimester only, 19 % during the first and second or third trimester, and 5 % were exposed in the second and third trimester only.

Furthermore, the mean daily maternal dose of topiramate was 97 mg, and maternal treatment was predominantly as migraine prophylaxis, for which generally a lower dose is used compared with epilepsy treatment.

Overall, this study is considered as well conducted but precision of estimates is modest. The study also includes important limitations, including the exposure to topiramate mainly in the lower dose range and occurring predominantly in the first trimester, while NDDs is thought to occur also following exposure during the second and third trimesters. In addition, there was a short duration of follow-up compared to the studies above. These limitations decrease the possibility to characterise the potential adverse effects of topiramate exposure during pregnancy on child neurodevelopment.

Hernandez-Diaz S et al., 2022

An abstract of the study by Hernandez-Diaz et al., 2022 was presented at the 38th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) in Denmark in August 2022 and further evaluated in the current review. Further details of the study were made available to PRAC in the course of this procedure for further consideration.

The study by Hernandez-Diaz et al., 2022 is a cohort study of pregnant women and their children nested in the Medicaid Analytic eXtract (2000–2014, N=2.07 million publicly insured pregnancies) and the IBM MarketScan (known now as Merative MarketScan) Research Database (2003–2015, N=1.31 million commercially insured pregnancies). Exposure to specific AEDs was defined based on ≥1 prescription fills from gestational week 19 until delivery (period of synaptogenesis). Unexposed pregnancies were defined as those without any AED prescription fills from three months before pregnancy until delivery. Liveborn infants were followed until diagnosis of a NDD, disenrollment, death or end of the study. Specific NDDs were studied as ASD, ADHD, learning difficulty, speech or language disorder, developmental coordination disorder, ID and behavioural disorder.

Topiramate exposed pregnancies were compared to unexposed pregnancies in women from the general population and with epilepsy. HR and 95% CIs were estimated using Cox proportional hazards regression with propensity score weighting to adjust for treatment indication (e.g. epilepsy, migraine, bipolar disorder), concomitant medications, proxies for lifestyle behaviour, healthcare utilisation, demographics, and other comorbidities. Estimates from each data source were combined using a fixed effects meta-analysis model. The validation of NDD diagnoses was conducted within these medical records as described in Straub et al., 2021.

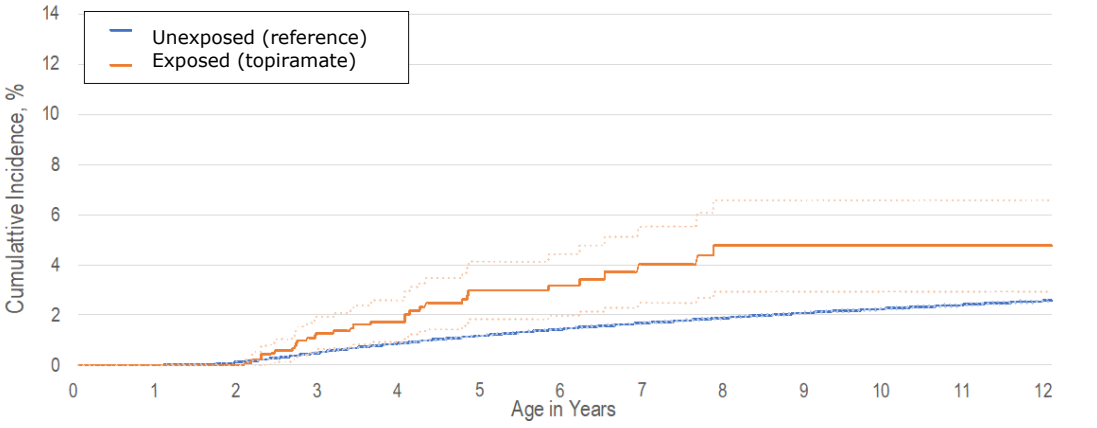
Overall, 2,469 pregnancies exposed to topiramate were identified and among those 1,030 pregnancies were in mother who had epilepsy. For lamotrigine monotherapy, there were 7,130 pregnancies and among those 3,134 pregnancies were in mothers who had epilepsy. See table 3 below.

Table 3. Study population and number of exposed pregnancies

	Full Cohort			Epilepsy Restricted		
	MAX	MarketScan	**Combined**	MAX	MarketScan	**Combined**
TOTAL	2503308	1789231	4292539	22286	6666	28952
No_AED (Ref)	2433177	1766619	4199796	7245	1570	8815
Lamotrigine monotherapy (Ref)	4038	3092	7130	1576	1558	3134
Lamotrigine (any)	4987	3477	8464	2323	1882	4205
Topiramate (any)	1750	719	2469	730	300	1030
Valproate (any)	1236	156	1392	687	113	800

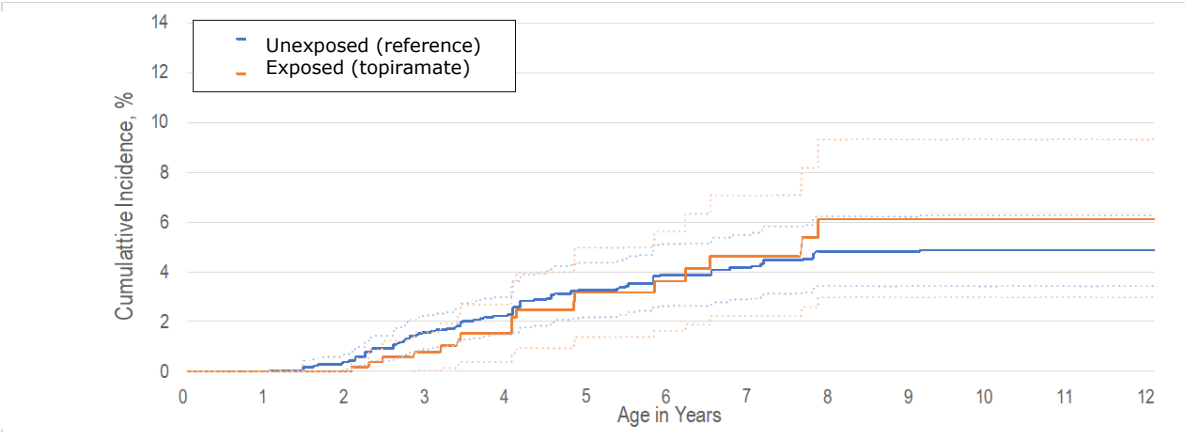
For children not exposed to an AED during pregnancy, the cumulative incidence by 8 years of age of ASD was about 2%. Figure 3 shows the unadjusted cumulative incidence of ASD for topiramate and the reference group in the full cohort. Figure 4 shows the adjusted cumulative incidence of ASD for topiramate and the reference group of the epilepsy cohort.

Figure 3. Cumulative incidence of ASD for topiramate and the reference group in the full cohort (crude)



Exposed													
Cum. Cases	0	0	0	14	18	26	27	30	32	32	32	32	32
At Risk	2469	1943	1308	925	705	538	417	315	233	158	117	82	58
Cum. Incidence	0.00	0.00	0.00	1.27	1.75	2.97	3.19	4.00	4.75	4.75	4.75	4.75	4.75
Reference													
Cum. Cases	0	0	2916	10165	15176	18436	20649	22075	23071	23769	24213	24514	24716
At Risk	4199796	3208209	2175080	1560505	1179432	904264	690431	528886	401396	298985	218041	154211	104155
Cum. Incidence	0.00	0.00	0.12	0.51	0.87	1.18	1.45	1.68	1.89	2.09	2.26	2.42	2.57

Figure 4. Adjusted cumulative incidence of ASD for topiramate and the reference group of the epilepsy cohort



Exposed													
Cum. Cases	0	0	0	4	7	12	13	15	17	17	17	17	17
At Risk	1030	809	562	430	325	249	207	164	118	82	59	46	37
Cum. Incidence	0.00	0.00	0.00	0.79	1.54	3.18	3.62	4.63	6.15	6.15	6.15	6.15	6.15
Reference													
Cum. Cases	0	0	2.48107064	8.23906779	10.7391388	13.6041906	14.8271652	15.284738	16.1102168	16.1102168	16.137705	16.137705	16.137705
At Risk	1055.827	838.676248	559.176538	404.443924	299.971355	231.182156	171.678581	135.05737	100.692817	70.7862685	53.9079617	35.0179572	20.9423788
Cum. Incidence	0.00	0.00	0.38	1.57	2.25	3.26	3.87	4.17	4.82	4.82	4.86	4.86	4.86

In table 4 below, HR for the cumulative incidence at 8 years of age of ASD is shown.

Table 4. Cumulative incidence at age 8 of ASD; HR with 95% CI, expressed as lower confidence limit (LC) and upper confidence limit (UCL)

Population	Exposed	Adjusted	Risk Exposed	Risk No-AED	HR	LCL	UCL
Full	Topiramate	No	4.75	1.89	2.17	1.54	3.07
Epilepsy	Topiramate	No	6.15	4.21	1.16	0.70	1.94
Epilepsy	Topiramate	Yes	6.15	4.82	0.97	0.56	1.68
Full	Lamotrigine	No	2.73	1.89	2.16	1.76	2.64
Epilepsy	Lamotrigine	No	2.75	4.21	1.01	0.72	1.41
Epilepsy	Lamotrigine	Yes	2.75	4.28	0.94	0.63	1.42
Full	Valproate	No	6.83	1.89	3.69	2.68	5.07
Epilepsy	Valproate	No	10.51	4.21	2.53	1.70	3.78
Epilepsy	Valproate	Yes	10.51	3.91	2.68	1.61	4.44

The patterns observed were similar for all specific NDDs studied. Overall, the associations seem to be largely explained by the indications and other related factors.

Discussion

The study by Hernandez-Diaz et al., 2022 is considered of particular importance in this review given the large number of pregnancies exposed to topiramate, an appropriate design, also analysing data for lamotrigine as well as valproate which put data into context, a relevant length of children follow-up

over more than 8 years as well as a notable proportion of relevant events and an appropriate attention to bias control.

Overall, the pattern from this study is in line with that seen in the studies conducted in the Nordic countries by Bjørk et al., 2022 and Dreier et al., 2023 when comparing neurodevelopmental outcomes for children exposed in utero to topiramate with unexposed children from the general population. However, when restricting the comparisons to women with epilepsy, the aHR for the cumulative incidence of ASDs at 8 years of age was not increased for children whose mothers had epilepsy, and who had been exposed to topiramate or lamotrigine during pregnancy, while an increased HR remained for valproate exposed children. See table 4 above. The results for lamotrigine users in epilepsy indications are of particular relevance for addressing confounding by indication. The reason is that this substance is not considered to increase the risk for major malformations, based on a large amount of data, and does not seem to pose an increased risk of neurodevelopmental outcomes in children exposed in utero. This is further supported by data from this study, as well as by Bjørk et al. 2022, in comparisons with the group of non-treated women with epilepsy. Importantly, these results did not suggest a difference in HRs between topiramate and lamotrigine exposed patients in the epilepsy indication. This supports the fact that other factors than topiramate exposure explain, at least partially, the increased occurrence of neurodevelopmental outcomes when comparing children exposed in utero to topiramate with non-exposed children from the general population. In summary, the study did not find an increase cumulative incidence of these outcomes by 8 years of age in approximately 1,000 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED.

2.3.2. Major congenital malformations

The present assessment also included a review of new evidence on major congenital malformations (MCMs) since the most recent PSUSA (DLP: 19 January 2022) procedure where this known risk was evaluated. As already described in the product information, it is well established that topiramate can cause foetal harm when administered to a pregnant woman. Clinical data from pregnancy registries show that infants exposed to topiramate monotherapy have an increased risk of congenital malformations (particularly cleft lip/palate, hypospadias and anomalies involving various body systems) following exposure during the first trimester. Date from the North American Antiepileptic Drug Pregnancy registry on topiramate monotherapy, already reflected in the product information, show an approximate 3-fold higher prevalence of MCMs (4.3%), compared with a reference group not taking AEDs (1.4%). The following study by Cohen et al., 2023 further confirms this picture and is reviewed below.

Cohen JM et al, 2023

The study by Cohen et al., 2023 is a Nordic register-based cohort study with the objective to examine the comparative safety of ASM monotherapy in pregnancy with respect to the risk of MCMs, overall and by MCM subtypes. All documented pregnancies (singleton and multiple births, live births and stillbirths) in the general population of the Nordic countries were included in the study, i.e. Denmark (1997-2017), Finland (1996-2016), Iceland (2003-2017), Norway (2004-2020) and Sweden (2006-2019).

ASM-exposed pregnancies were defined as those in which the mother had filled one or more prescriptions for ASMs during the first trimester. The requirement for monotherapy was that the mother took only one ASM substance from 90 days before her last menstrual period to the end of the

first trimester. One secondary (sensitive) exposure definition included pregnancies with filled prescriptions only in the 30 days prior the last menstrual period to capture the first trimester. A further secondary (specific) exposure definition required at least two prescriptions to be filled during pregnancy, with at least one in the first trimester. Women exposed to multiple ASMs in the first trimester were excluded from the study. ASM-unexposed pregnancies were defined as pregnancies in which the mother had not filled a prescription for any ASM from 90 days before the last menstrual period to the end of the first trimester.

The primary outcome was MCM diagnosed within one year of birth recorded in the medical birth, patient, malformation or death register. The definition of MCMs was aligned as closely as possible with the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) 1.4 classification.

Among 4,917,523 pregnancies, 5,874 were excluded due to exposure to strong teratogenic medications, 3,759 due to ASM polytherapy and 12,898 due to chromosomal anomaly, genetic syndrome, or teratogenic infection. Of the pregnancies considered, 15,906 (0.3%) were exposed to ASM monotherapy, there of 8,339 to lamotrigine, 2,674 to carbamazepine, 2,031 to valproate, 1,313 to oxcarbazepine, 1,040 to levetiracetam, and 509 to topiramate.

Epilepsy was the most common indication for each of the ASM monotherapies (47.0-98.9%). Of the ASMs, topiramate was used least frequently for the treatment of epilepsy (47 %) but most frequently for the treatment of migraine (23%), whereas the other ASMs were prescribed infrequently for migraine (between 1.8% and 4.9%).

Most pregnancies exposed to ASM monotherapy had a higher prevalence of any MCM than the ASM-unexposed pregnancies with about 30.4 MCMs per 1,000 pregnancies (96% CI 30.2-30.6), with the highest prevalence showed for valproate or topiramate use during pregnancy. Lamotrigine-exposed infants showed no increased risk of MCM compared to ASM-unexposed after adjusting for all confounders. Lamotrigine can also be seen as an internal active comparator. Compared to lamotrigine monotherapy, topiramate was associated with an approximately 2-fold increased risk of MCM in both minimally adjusted and fully adjusted models (e.g. fully adjusted primary model: topiramate adjusted risk ratio (aRR) 1.81, 95% CI 1.26–2.60). In the secondary (specific) analysis, the fully aRR was increased for topiramate compared to the primary analysis (fully aRR primary: 1.81 vs. specific: 2.67). Compared to the unexposed population the prevalence rate of MCM for topiramate was 2–fold higher in the primary analysis (3.04% vs. 6.29 %) and 3-fold higher in the specific analysis (3.04 % vs. 9.51 %).

Finally, an increased risk was observed with topiramate only with the high-dose (>125-600 mg: aRR 2.69, 95% CI 1.65-4.38), but not with lower dose (25–125 mg: aRR 0.79, 95% CI 0.42-1.49).

Discussion

The study by Cohen et al, 2023 presents several strengths. One of the main strengths is the size of the study and the representativeness of the Northern European population on a 15-20 year-long period. Other strengths include the definition of the analysed cohorts and the quality of the performed primary analyses which is confirmed by sensitivity analyses.

In the primary analysis, the prevalence rate of MCMs for topiramate is 6.29 % corresponding to a 2-fold higher rate compared to the background prevalence rate of 3.04 % in the unexposed population. In the specific analysis, the prevalence rate of MCMs for topiramate was even increased to a 3-fold higher rate compared to the unexposed population. The observed 2-fold increased risk of MCMs for topiramate is expected to be causal and this is in line with previous evaluations and the current product information. Assuming that the specific analysis better captures cases with actual exposure to

topiramate during pregnancy, this further reinforces the information already reflected in the current product information.

With regard to dose relationship, lower doses of topiramate may point towards a reduced risk of MCM. However, the analysed strata were rather small (312 pregnancies exposed low-dose vs. 170 pregnancies exposed to high-dose) and resulted in a low precision of the point estimates. A dose-dependent risk for MCMs is already described in the product information.

In summary, the study by Cohen et al., 2023 confirms the known teratogenic risk of topiramate. It also provides a consistent picture of the relative increased risk in line with the existing information of the product information of topiramate-containing products. However, despite the relative frequencies are the same in this study and those already described in the product information from the North American Antiepileptic Drug pregnancy registry (2- to 3-fold increase), the absolute numbers both for the control group (3% vs 1.4%) and the topiramate exposed pregnancies (6-9% depending on exposure definition vs 4.3%) are higher, than the prevalence data currently reported in the product information.

2.3.3. Foetal growth restriction

As already described in the product information, an increased prevalence of being small for gestational age (SGA, defined as birth weight below the tenth percentile corrected for their GA stratified by sex) has been observed with topiramate. To further substantiate the factual information in the product information for these adverse outcomes, the PRAC reviewed more recent and relevant evidence on foetal growth restriction such as low BW and SGA namely a study from Hernandez-Diaz et al., 2017. This study evaluated the effects of epilepsy and AEDs used during pregnancy on foetal growth and preterm delivery.

Hernandez-Diaz S et al., 2017

The study by Hernandez-Diaz et al., 2017 includes singleton liveborn infants born to women enrolled in the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2016. Data were collected prospectively through telephone interviews. The prevalence of preterm birth (<37 weeks) and SGA among infants exposed prenatally to AEDs when used by women with epilepsy (WWE) or women without epilepsy (WWOE) was compared with that among infants unexposed to AEDs and born to WWOE. Multivariate log-binomial regression models were used to estimate RRs and 95% CIs.

The study population included infants born to 6,777 AED-WWE, 696 AED-WWOE, and 486 no-AED-WWOE. The risk of prematurity was 6.2% for no-AED-WWOE, 9.3% for AED-WWE (RR 5 1.5, 95% CI 5 1.0–2.1), and 10.5% for AED-WWOE (RR 5 1.5, 95% CI 5 1.0–2.4). Prenatal exposure to AEDs in WWE and WWOE was associated with a mean lower BW of 110 and 136g, respectively, as compared to no-AED-WWOE.

The prevalence of SGA was 5.0% for no-AED-WWOE, 10.9% for AED-WWE (RR 5 2.0, 95% CI 5 1.3–3.0), and 11.0% for AED-WWOE (RR 5 1.9,95% CI 5 1.2–2.9). Within the users of AEDs in monotherapy, the prevalence of SGA ranged from 7.3% for lamotrigine to 18.5% for topiramate.

The authors concluded that women on AEDs during pregnancy, whether in the epilepsy indication or for other neuropsychiatric indications, are at a higher risk of delivering prematurely and giving birth to SGA newborns.

Discussion

The North American Antiepileptic Drug Pregnancy Registry is an established data source for various outcomes in relation to in utero exposure to AEDs. This study provides additional absolute figures on the magnitude of the known risk of SGA following in utero exposure to topiramate. The risk of SGA in children of women receiving topiramate was 18 % compared with 5 % in children of women without epilepsy not receiving an AED.

The results from this study provide absolute data on prevalence of these outcomes data for topiramate and the comparator group, which currently are only briefly mentioned in the product information.

2.4. Pharmacokinetic aspects

Three prospective, observational studies (Westin et al., 2009, Voinescu et al., 2018, Pennell et al., 2022) exploring the impact of pregnancy on serum concentrations of topiramate in pregnant women treated with topiramate were considered of relevance in this review. All of them included a relatively small number of pregnant women dosed with topiramate, with a limited number of pharmacokinetic samples taken on each sampling occasion, and at different time points post dosing. In addition, a large variability in dose-normalised concentrations were observed between subjects. Although a trend towards a decrease in dose-normalised concentrations of topiramate during pregnancy is observed, the limitations of the studies did not allow to draw any firm conclusions.

With regard to the risk of interaction between topiramate and systemic hormonal contraceptives, the current respective product information of the originator medicinal product containing topiramate monocomponent as well as for the topiramate/phentermine-containing product reflects that topiramate affects the exposure to the tested components of a combined oral contraceptive product containing norethindrone/ethinyl estradiol based on various interaction studies. Furthermore, the respective product information for the monocomponent products and the fixed-dose combination product states that while the clinical significance of the changes observed is not known, the possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking these medicinal products.

Thus, these data raise concerns that topiramate may decrease the efficacy of hormonal contraceptives. In addition, the product information of several systemic hormonal contraceptives containing a progestin as a monocomponent, states that topiramate may increase the clearance of progestin due to enzyme induction. Further evidence from the literature (Lazorwitz et al., 2021; Rowlands et al., 2019) refers to interaction between topiramate and progestin in implants. As topiramate is a weak inducer of cytochrome P450 3A4 (CYP3A4), there is a mechanistic support that the metabolism of systemically administered progestins may be induced (Brodie et al., 2013) as expressed in the product information of such implants.

As a precautionary measure, it is therefore recommended to add a barrier method of contraception for women using systemic hormonal contraceptives to ensure highly effective contraception.

It is also important to note that the product information of the topiramate/phentermine-containing product states that contraception should continue for at least 4 weeks after treatment discontinuation. This is based on the need to cover at least one menstrual cycle and to ensure that topiramate has been adequately cleared from the body, taking into account its terminal half-live of 50 hours approximately. Since 5 to 7 half-lives are generally needed, this corresponds to approximately 14 days. To allow additional reassurance, a 4-week period of continued contraception after stopping topiramate treatment is considered appropriate. This statement is relevant to all topiramate-containing products.

2.5. Non-clinical aspects

Studies on neurodevelopmental outcomes in offspring were carried out in pregnant rats which were prenatally exposed to varying levels of topiramate, e.g. in comparison with lamotrigine (Dag et al., 2014), water (Mishra, 2010), lamotrigine, phenobarbital or levetiracetam (Manent et al., 2008), while other studies were more focused on identifying potential molecular mechanisms of NDDs. Different study designs, different doses and different ways of applications were used in these studies. The mechanisms proposed are not considered specific for topiramate. Overall, these data are considered of limited relevance for further understanding of whether topiramate treatment in utero increases the risk for NDDs.

3. Expert consultation

The PRAC consulted the Scientific Advisory Group on Neurology (SAG-N) on 01 March 2023 which provided advice on a number of issues.

Regarding available epidemiological data on in utero exposure to topiramate and the risk for NDDs, the experts agreed that the studies present some evidence supporting an association between topiramate and the risk for developmental disorders. However, the experts noted that there are limitations (e.g. small number of cases, indication bias, risk of exposure misclassification) and particularly, uncertainties about the minimum dose/exposure that could imply a risk. While the available evidence was considered enough to provide further information to healthcare professionals and patients about the potential risk, it is not sufficient at this stage for supporting a contraindication on the use of topiramate in epilepsy.

With respect to the place in therapy of topiramate and its medical need in the treatment of epilepsy in female children and adolescents, in WCP as well as in pregnancy, the experts agreed that topiramate is neither the first line drug for epileptic disorders nor the only option for any particular syndrome. The experts agreed that it is possible to switch from topiramate to any other anti-epileptic drug with a relatively low and manageable risk for the epileptic patient. However, it was noted that there is no clear scientific evidence supporting a switch between AEDs during pregnancy, the best level of evidence comes from expert opinions and not from data. Depending on the type of epileptic seizures, the experts highlighted few therapeutic options including lamotrigine and/or levetiracetam.

To the question on a possibility to restrict prescription of topiramate, the experts considered that restricting the prescription is not a useful measure. For epilepsy, topiramate is already prescribed by neurologists. For migraine, the restriction could either limit their use when needed or would imply additional burden for the specialists.

With regard to the implementation of risk minimisation measures beyond the product information, the experts were overall in favour of increasing awareness on the risks. The implementation of healthcare professional and patient/caregiver guides was supported. The implementation of a patient card, text warning on the outer packing and the annual re-assessment is supported by patient representatives but was not fully endorsed by all experts.

Finally, the experts agreed that regardless of the indication (on vs. off-label) the same level of information should be provided to all potential prescribers.

4. Benefit-risk balance

The PRAC considered that the data reviewed in the context of this referral procedure do not bring into question the efficacy of topiramate-containing products as no new data were made available to change the already established benefit of the medicinal products in the respective approved indications.

With respect to risks, the PRAC reviewed the totality of the data submitted during this review in relation to NDDs, and further reviewed new relevant data on the known risk of MCMs. These data included the responses submitted in writing by the MAHs, additional available literature and the outcome of the consultation with the Scientific advisory group on Neurology.

Regarding NDDs, the Committee considered three pharmaco-epidemiological studies of major relevance for assessing this potential risk, because these studies were undertaken in useful data sources, had relevant designs and were well conducted.

The study by Bjørk et al., 2022 was undertaken in well-established national population-based healthcare registers from the five Nordic countries, which have similar healthcare contexts and health data structures. For topiramate, a higher prevalence of NDD outcomes was seen in children of mothers with epilepsy, who had been exposed to topiramate during pregnancy compared to children of unexposed mothers with epilepsy. Further review of the available data suggested that a substantial part of this increased occurrence of NDD outcomes is related to strong selection mechanisms behind the low proportion of pregnancy exposures to topiramate, although a causal role of topiramate for the development of NDDs is considered possible following prenatal exposure. However, it was not possible to determine the portion of the estimated relative risk that is actually due to topiramate or due to the underlying patient and/or disease characteristics, thus the evidence remains weak overall.

The study by Dreier et al., 2023 was undertaken in essentially the same dataset as the study by Bjørk et al., 2022 but focused on mothers with epilepsy only. In this study, an increased occurrence of ADHD was observed for children exposed in utero to topiramate compared with mothers/children unexposed to an AED. Further, increased point estimates for ASD and ID were also seen in this study, although they were not statistically significant. Taken together, the studies by Bjørk et al., 2022 and Dreier et al., 2023 suggest a 2- to-3-fold higher prevalence of ASD, ID or ADHD in almost 300 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED. Similar to Bjørk et al., 2022, it remains also unclear for this study to what extent this higher risk of NDDs is caused by topiramate exposure or other risk factors more prevalent in mothers exposed to topiramate. Nevertheless, the PRAC considered that these data are sufficiently strong to be reflected in the product information.

The study by Hernandez-Diaz et al., 2022 was a cohort study in pregnant women and their children conducted in U.S. healthcare utilisation databases. Overall, 2,469 pregnancies exposed to topiramate were identified, and among those, 1,030 pregnancies were in mothers who had epilepsy. Data for both lamotrigine and valproate were also analysed in this study. Lamotrigine exposures are of particular relevance to address confounding by indication, since this substance is widely considered to be safe for the developing foetus. These analyses included 7,130 pregnancies exposed to lamotrigine, among which 3,134 were in mothers who had epilepsy. The increased risk of NDDs observed in children of pregnant mothers exposed to valproate may support analyses of assay sensitivity with its well-established increased risk for NDDs. For valproate, expected increases in HRs for NDD outcomes were seen. However, this study did not show increased HRs for neurodevelopmental outcomes in children of women with epilepsy exposed to topiramate or to lamotrigine in utero. This supports that other factors than topiramate exposure explain, at least partially, the increased occurrence of neurodevelopmental outcomes when comparing children exposed in utero to topiramate with non-exposed children from the general population. The PRAC considered that this study is of particular importance in this review given

the large number of pregnancies exposed to topiramate, its appropriate design, the relevant length of children follow-up over 8 years, a notable proportion of relevant events and an appropriate attention to bias control.

Overall, while no firm conclusion could be drawn on the risk of NDDs in view of the inconsistent results of the currently available data, the PRAC concluded that NDDs should be considered as an important potential risk for topiramate use during pregnancy and that the data from these three observational studies should be reflected in the product information of all topiramate-containing products.

With regard to congenital malformations and foetal growth restrictions, these are well established identified risks after topiramate in utero exposure and are already reflected in the product information of all topiramate-containing products. Additional evidence from the studies by Cohen et al., 2023 and Hernandez-Diaz, 2017 further confirm the risks for serious adverse birth outcomes with topiramate and provide further clarity on the magnitude of these risks. Available data show that in women who took topiramate during pregnancy, 4 to 9 out of every 100 children had birth defects, compared with 1 to 3 out of every 100 children born to women who did not take such treatment. Further, around 18 children in every 100 were smaller and weighed less than expected at birth when mothers had taken topiramate during pregnancy, compared with 5 children in every 100 born to mothers without epilepsy and not taking antiepileptic medication. The PRAC was of the view that these results should be reflected in the product information of all topiramate-containing products.

Regarding risk minimisation measures in relation to these risks, the PRAC confirmed the measures already in place and recommended strengthening the contraindications further. The Committee also agreed on the implementation of further risk minimisation measures and tools in the form of a pregnancy prevention programme. A number of amendments of the exact wording of these measures was also made in the product information to provide further clarity.

Thus, the PRAC confirmed the contraindications in pregnancy when topiramate is used as migraine prophylaxis or for the treatment of obesity or overweight. Further, in all indications, advice on pregnancy testing before treatment of WCP and on the need for using a highly effective contraceptive method are already implemented. Statements about the necessity for women to be fully informed about the risks with use of topiramate during pregnancy are also available.

In addition, the Committee recommended the implementation of contraindications in the epilepsy indication. Although the SAG-N did not consider that there was sufficient available evidence to support a contraindication on the use of topiramate during pregnancy and in WCP for the treatment of epilepsy, the PRAC considered that a contraindication in pregnancy is warranted unless there is no suitable alternative treatment, as well as in WCP not using highly effective contraception. For the latter group, the PRAC agreed to introduce an exception for women for whom there is no suitable alternative but who plan a pregnancy and are fully informed about the risks of taking topiramate during pregnancy. This is in line with the SAG-N position.

In the epilepsy indication, the PRAC also confirmed the current advice to consider alternative therapeutic options in WCP, and the information about the risks of uncontrolled epilepsy to the pregnancy. The PRAC confirmed the current pieces of advice, namely the need for a preconception visit for women planning a pregnancy to reassess treatment with topiramate and consider other therapeutic options, as well as the need for patients to inform their doctor straight away in case of pregnancy and that patients should decide together with their doctor whether topiramate treatment should continue during pregnancy.

Moreover, the PRAC agreed that topiramate treatment of female children and WCP should be initiated and supervised by a physician experienced in the treatment of epilepsy or migraine. As highlighted by the SAG-N, topiramate is neither the first line medicine for epileptic disorders nor the only option for

any particular syndrome. Therefore, alternative therapeutic options should be considered in female children and in WCP. For the topiramate/phentermine fixed dose combination product, the PRAC confirmed the current recommendation that treatment should be initiated and supervised by a clinician experienced in obesity treatment. In all indications, the need for treatment with topiramate should be reassessed at least annually to confirm that the pregnancy prevention programme is adhered to.

Based on the review of a potentially clinically relevant interaction between topiramate and systemic hormonal contraceptives, the PRAC recommended as a precautionary measure that women using systemic hormonal contraceptives should be advised to also use a barrier method to ensure highly effective contraception. Based on the need to cover at least one menstrual cycle and to ensure that topiramate has been adequately cleared from the body, the Committee also recommended to update the product information of all topiramate-containing products to reflect the need to continue contraception for at least 4 weeks after stopping treatment.

In the indications covering the use of topiramate in female children with epilepsy or as migraine prophylaxis, it is further emphasised that prescribers must ensure that parent(s)/caregiver(s) of female children understand the need to contact a specialist once the child experiences menarche. At that time, the patient and parent(s)/caregiver(s) should be provided with comprehensive information about the risks due to topiramate exposure in utero and about the need to use highly effective contraception as soon as relevant.

Moreover, the Committee considered it necessary to implement additional risk minimisation measures and tools as educational materials for healthcare professionals in the form of a healthcare professional guide, including a risk awareness form to be completed with the patient, and for patients in the form of a patient guide. These measures are put in place to increase awareness of healthcare professionals and patients on the risks of adverse outcomes after in utero exposure to topiramate, and to highlight the measures of the pregnancy prevention programme aiming at minimising pregnancy exposure during treatment with topiramate-containing products.

The Committee also recommended a patient card to be placed inside or affixed to one side of the outer packaging as well as a warning on the outer packaging to warn WCP on the risks to be pregnant while using topiramate. The PRAC noted that the use of a pictogram was discussed by the SAG-N but no consensus was reached on this possible measure. The PRAC considered that visual symbols can be interpreted differently across Member States. The PRAC further noted that, as part of their remit, the National Competent Authorities can decide to implement a pictogram at national level as relevant. It was also noted that the use of boxed warnings in the product information can be decided by the National Competent Authorities at national level as relevant.

Finally, the Committee considered that the MAHs of topiramate-monocomponent products should be requested to implement additional pharmacovigilance activities in the form of a drug utilisation study to evaluate the effectiveness of the implemented risk minimisation measures with a particular focus on preventing pregnancies and on further characterising the prescribing patterns for topiramate in the target populations for pregnancy prevention. Furthermore, the MAHs of topiramate-monocomponent products should carry out surveys amongst healthcare professionals and patients to assess their knowledge and behaviour as applicable with regard to the risks of topiramate use during pregnancy and the measures implemented to prevent pregnancy as well as receipt/use of educational materials as part of the pregnancy prevention programme. The protocols for the drug utilisation study and surveys should be submitted to the PRAC in accordance with Article 107n(1) of Directive 2001/83/EC according to agreed timelines.

A direct healthcare professional communication (DHPC) was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures agreed as described above.

In view of the above, the Committee considered that the benefit-risk balance of topiramate-containing products remains favourable subject to the agreed amendments to the product information, the agreed conditions to the marketing authorisations as applicable, and other risk minimisation measures.

5. Summary of new activities and measures

5.1. Risk management

The Committee, having considered all information and data submitted in the procedure, recommended a series of risk minimisation measures to minimise the risks of MCMs, foetal growth restrictions, NDDs due to in utero exposure to topiramate. Furthermore, additional pharmacovigilance activities were recommended to characterise the effectiveness of these measures.

The MAHs should update their risk management plan (RMP) or implement a new one to reflect the pharmacovigilance activities and additional risk minimisation measures listed below, as applicable, and submit it to the relevant National Competent Authorities through an appropriate procedure.

5.1.1. Safety concerns

The Committee considered that MCMs should be added as an important identified risk and NDDs as an important potential risk.

5.1.2 Risk minimisation measures

5.1.2.1. Routine risk minimisation measures

Amendments *to* the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information are necessary in order to minimise the risks of NDDs, MCMs and foetal growth restriction associated with the use of topiramate-containing products during pregnancy. These changes include amendments to sections 4.2, 4.3, 4.4, 4.5 and 4.6 of the SmPC.

Section 4.2 of the SmPC is updated to include that treatment with topiramate should be initiated and supervised by a physician experienced in the management of epilepsy or migraine, or in obesity for the fixed-dose combination product. In addition, alternative therapeutic options should be considered in WCP and female children as applicable and the need for topiramate treatment in these populations should be reassessed at least annually.

Section 4.3 of the SmPC is updated to also include a contraindication in pregnancy for the epilepsy indication unless there is no suitable alternative treatment. A contraindication is also implemented for WCP with epilepsy not using highly effective contraception, together with an exception for women with no suitable alternative but planning pregnancy and informed about the risks.

Section 4.4 of the SmPC is updated with statements of a pregnancy prevention programme to ensure that a pregnancy testing should be performed before initiating treatment with topiramate in a WCP and that the patient is fully informed and understand the risks related to the use of topiramate during pregnancy. For female children taking topiramate in relevant indications, parent(s)/caregiver(s) should be informed and understand the need to contact a specialist once the child experiences menarche and

comprehensive information provided about the risks due to topiramate exposure in utero, and the need for using highly effective contraception as soon as relevant.

In addition, section 4.5 of the SmPC is updated with regard to interaction between topiramate and systemic hormonal contraceptives in order to advise women using systemic hormonal contraceptives to add a barrier method of contraception.

Finally, section 4.6 of the SmPC is updated to include further evidence and data from observational studies on MCM, foetal growth restrictions and on NDDs together. Some amendments of the currently available wording are also made for clarity.

The package leaflet is amended accordingly.

As part of the labelling, a warning on the outer packaging is added, as well as a patient card to be placed inside or affixed to one side of the outer packaging. These are implemented to warn WCP on the risks to be pregnant while using topiramate. The patient card lists specifically contraception and pregnancy prevention measures.

The black symbol and corresponding statements are added to the product information to reflect the fact that topiramate-monocomponent products are being added on the additional monitoring list.

5.1.2.2. Additional risk minimisation measures

Additional risk minimisation measures and tools in the form of educational materials are necessary in order to increase awareness of healthcare professionals and patients on the risks of adverse outcomes after in utero exposure to topiramate, and on measures needed to be taken to minimise these risks. These measures are referred to as a pregnancy prevention programme.

For topiramate monocomponent products, the PRAC requests the implementation of educational materials for healthcare professionals and patients. For the topiramate/phentermine-containing product, amendments to existing materials are requested. These educational materials contain the following elements:

- Healthcare professional guide:

  The guide is implemented to remind that children exposed in utero to topiramate have a higher risk for congenital malformations, low BW and being SGA and may have an increased risk for NDDs. This guide also aims at reinforcing the measures of the pregnancy prevention programme including the contraindications in pregnancy and in WCP under certain conditions across all indications, contraceptive measures and pregnancy planning information. The importance of the patient being fully informed, and to understand these risks is also highlighted.

  The guide also includes a risk awareness form intended as an additional support for informing on the risks for serious birth outcomes after exposure in pregnancy and for use on a regular reassessment of topiramate use in clinical practice in WCP. This form needs to be digitally editable in order to facilitate its use and should be completed with the patient at initiation, at annual review, and if the patient plans a pregnancy or has become pregnant.

- Patient guide:

  The guide is implemented to remind that children exposed in utero to topiramate have a higher risk for congenital malformations, low BW and being SGA and may have an increased risk for NDDs. This guide also aims at reinforcing the measures of the pregnancy prevention programme.

The format of the healthcare professional guide and the patient guide as educational materials is left at the discretion of the National competent Authorities in order to select the most suitable format in the

relevant territory taking into consideration the existing material(s) and the characteristics of the respective national healthcare system. The final version of these materials must be agreed with the National Competent Authorities in each Member State.

5.1.3. Pharmacovigilance activities

5.1.3.1. Drug utilisation study

The MAHs for topiramate monocomponent products shall conduct and submit the results of a drug utilisation study as a non-interventional post-authorisation safety study in order to evaluate the effectiveness of the implemented risk minimisation measures with a particular focus on preventing pregnancies and on further characterising the prescribing patterns for topiramate in the target populations for pregnancy prevention.

This study is imposed as a condition to the marketing authorisations and reflected as category 1 in the RMP. The protocol shall be submitted to the PRAC for assessment within 6 months from the CMDh agreement in case of a position adopted by consensus or the Commission Decision as applicable. Interim report(s) should be submitted to the EMA/PRAC every 24 months after endorsement of the study protocol and the final study report should be submitted to the EMA/PRAC within 48 months after endorsement of the study protocol.

These studies should cover several EU Member States and be representative of the European population.

The MAHs are strongly encouraged to conduct a joint study.

5.1.3.2. Survey

The MAHs for topiramate monocomponent products shall conduct and submit the results of a non-interventional post-authorisation safety study as a survey with two parts:

- one part among healthcare professionals in order to assess their knowledge and behaviour with regard to the measures to be taken to prevent pregnancies as well as receipt/use of DHPC and educational materials.
- one part among patients in order to assess their knowledge with regard to the risks of topiramate use during pregnancy and the measures implemented to prevent pregnancy as well as receipt/use of educational materials.

This study is imposed as a condition to the marketing authorisations and reflected as category 1 in the RMP. The protocol shall be submitted to the PRAC for assessment within 6 months from the CMDh agreement in case of a position adopted by consensus or the Commission Decision as applicable. The final study report should be submitted to the EMA/PRAC within 12 months after endorsement of the study protocol.

These studies should cover several EU Member States and be representative of the European populations.

The MAHs are strongly encouraged to conduct a joint study.

5.2. Direct Healthcare Professional Communications and Communication plan

The Committee considered that a DHPC is needed to inform healthcare professionals of the restrictions to prevent exposure during pregnancy with topiramate-containing products and associated risk minimisation measures referred to as a pregnancy prevention programme. The Committee also agreed on a communication plan. This communication should be distributed to neurologists, paediatricians, neuro-paediatricians, general practitioners, gynaecologists/obstetricians, specialists in internal medicine, midwives and pharmacists. The target group should be further defined at national levels in agreement with the respective National Competent Authorities.

All concerned MAHs are encouraged to liaise with National Competent Authorities to collaborate in order to prepare and circulate a single DHPC in each Member State.

6. Conditions to the marketing authorisations

The MAHs shall complete the below conditions, within the stated timeframe, and Competent Authorities shall ensure that the following is fulfilled:

In order to evaluate the effectiveness of the implemented risk minimisation measures with a particular focus on preventing pregnancies and on further characterising the prescribing patterns for topiramate in the target populations for pregnancy prevention, the MAHs of medicinal products containing topiramate as a monocomponent should conduct and submit the results of a drug utilisation study according to an agreed protocol.	Submission of the protocol to the PRAC in accordance with Article 107n(1) of Directive 2001/83/EC within 6 months from the CMDh agreement in case of a position adopted by consensus or the Commission Decision as applicable.
Interim report(s) should be submitted to the EMA/PRAC:	Every 24 months after endorsement of the study protocol.
The final study report should be submitted to the EMA/PRAC:	Within 48 months after endorsement of the study protocol.
In order to assess the knowledge of healthcare professionals and patients with regard to the risks of topiramate use during pregnancy and the measures to prevent pregnancies together with the receipt/use of the educational materials, the MAHs of medicinal products containing topiramate as a monocomponent should conduct and submit the results of a survey according to an agreed protocol. The survey part among healthcare professionals should also include the behaviour with regard to these risks and the measures to prevent pregnancies should include the receipt/use of the DHPC.	Submission of the protocol to the PRAC in accordance with Article 107n(1) of Directive 2001/83/EC within 6 months from the CMDh agreement in case of a position adopted by consensus or the Commission Decision as applicable.

The final study report should be submitted to the EMA/PRAC:	Within 12 months after endorsement of the study protocol.
The MAHs of all medicinal products should update their RMP or implement a new one to reflect the safety specification, pharmacovigilance activities and additional risk minimisation measures listed above, as applicable, and submit it to the relevant national Competent Authorities through an appropriate procedure.	Within 6 months from the CMDh agreement in case of a position adopted by consensus or the Commission Decision as applicable.

In addition, in accordance with Article 23 of Regulation (EC) No 726/2004, reference to the concerned products will be included in the list of products for additional monitoring. The relevant information as well as the pictogram (black triangle) will be added in the product information of medicinal products containing topiramate as monocomponent.

7. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data on topiramate-containing products.
- The PRAC reviewed the totality of the data submitted during this review in relation to the risk of NDDs, and further reviewed new relevant data on the known risk of MCMs. These data included the responses submitted in writing by the marketing authorisation holders, additional available literature and the outcome of the consultation with the Scientific advisory group on Neurology.
- The PRAC confirmed the current knowledge that MCMs and foetal growth restrictions are identified risks.
- The PRAC considered an increased risk of NDDs including ASD, ID or ADHD in children of mothers with epilepsy exposed to topiramate in utero as possible, compared with children of mothers with epilepsy not exposed to an AED. However, no final conclusion could be drawn at this stage because available data from epidemiological studies on this matter show inconsistent results. Therefore, NDDs should be considered as an important potential risk for topiramate use during pregnancy.
- In view of the new potential risk of NDDs, taken together with the known risks of MCMs and foetal growth restrictions, the PRAC concluded that there is a need to implement further risk minimisation measures in the form of a pregnancy prevention programme to reduce in utero exposure to topiramate.

  While the PRAC confirmed the contraindications in pregnancy and in WCP not using highly effective contraception in the indications of migraine and treatment of overweight, the Committee also recommended the implementation of contraindications in the epilepsy indication. In epilepsy, the PRAC also agreed that the contraindication in pregnancy is applicable unless there is no suitable alternative treatment, as well as in women of child-bearing potential not using highly effective contraception. However, for the latter group, an

exception is included for women for whom there is no suitable alternative but who plan a pregnancy and who are fully informed about the risks of taking topiramate during pregnancy.

- The PRAC also recommended additional risk minimisation measures comprising of a patient card and educational materials for healthcare professionals including a risk awareness form and for patients. A warning was also added to the outer packaging.
- The PRAC requested the MAHs of topiramate monocomponent products to conduct post-authorisation studies to evaluate the effectiveness of the measures implemented, and to assess the level of knowledge of healthcare professionals and patients on the risks and minimisation measures implemented as an outcome of this review.

In view of the above, the Committee considered that the benefit-risk balance of topiramate-containing products remains favourable subject to the agreed conditions to the marketing authorisations, the agreed amendments to the product information and other risk minimisation measures as described above.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for topiramate-containing products.

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