ABSTRACT

Title: Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey

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Rationale and Background

In the European Union (EU) and the United Kingdom (UK), topiramate mono-component products are used to treat seizures, epilepsy, and prevent migraine. In 2022, a study of population-based registries in five Nordic countries reported increased risk of neurodevelopmental disorders (NDDs) in children born to mothers with epilepsy exposed to topiramate in pregnancy compared to children whose mothers were unexposed (Bjørk et al. 2022). Given the potential increased risk of NDDs highlighted by this study and the known risk of congenital malformations, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in 2023 recommended updates to summaries of product characteristics (SmPC) and the implementation of additional risk minimization measures (RMMs) in the form of educational materials (EM) (health care professional guide and patient guide) under a Pregnancy Prevention Program. All these actions are henceforth collectively referred to as "newly implemented RMMs."

Before PRAC requested these newly implemented RMMs, topiramate was already contraindicated for migraine prevention in pregnancy and in women of childbearing potential (WOCBP) who are not using highly effective contraception. New contraindications now apply for the treatment of epilepsy. Specifically, topiramate is contraindicated (1) in pregnancy unless no suitable alternative treatment is available, and (2) in WOCBP not using highly effective contraception, with the only exception being a woman for whom there is no suitable anti-epileptic drug alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy.

To evaluate the impact of these RMMs, the PRAC (and concurrently the Medicines and Healthcare products Regulatory Agency (MHRA)) requested a healthcare professional (HCP) and patient survey to be conducted to assess the effectiveness of the newly implemented RMMs (i.e., updated label warnings and contraindications, HCP guide including risk awareness form, patient guide, patient card, and outer package warnings) in raising the awareness and understanding of this target population with respect to the safe use of topiramate.

Research Question and Objectives

Research Question

What is the impact of the newly implemented RMMs on the knowledge and self-reported behavior of HCPs who prescribe topiramate mono-component products and of patients treated with topiramate mono-component products in the EU and UK?

Objectives

To assess the awareness of:

- WOCBP treated with topiramate mono-component products with respect to the receipt of the EMs.

- HCPs with respect to the receipt of/access to Direct Healthcare Professional Communications (DHPC) and EMs for topiramate mono-component products.

To assess the knowledge of:

- WOCBP treated with topiramate mono-components products, with respect to risks associated with use of topiramate during pregnancy and measures to prevent exposed pregnancies.
- HCPs with respect to risks associated with use of topiramate during pregnancy and measures to prevent pregnancies among WOCBP exposed to topiramate mono-component products.

To assess the self-reported behavior of:

- WOCBP treated with topiramate mono-component products, with respect to measures to prevent exposed pregnancies.
- HCPs with respect to measures to prevent pregnancies among WOCBP exposed to topiramate mono-component products.

Study Design

This is a cross-sectional multinational survey conducted to assess knowledge and self-reported behavior of the patients and HCPs including general practitioners (GPs), specialists in internal medicine, other specialists managing epilepsy and/or migraine (including neurologists, general pediatricians, neuro-pediatricians, psychiatrists), obstetricians/gynecologists (OB/GYN), midwives, and pharmacists, with regards to the risks of topiramate use during pregnancy and the measures implemented to prevent pregnancy as well as receipt/use of the EMs in 6 European countries (5 EU member states and the UK).

Setting and Study Population

This study will be conducted among WOCBP in outpatient settings and HCPs through on-line questionnaires. The fieldwork will start no sooner than 12 months after the DHPC and EMs have been distributed in each country to enable the assessment of the newly implemented RMMs' effectiveness.

Each participant must satisfy the following criteria to be eligible for completion of the survey:

Patient inclusion criteria

- WOCBP (≥13 and ≤49 years of age) and being treated with topiramate mono-components products for migraine or epilepsy at the time of the survey.
- Interaction with an HCP related to topiramate for the treatment of migraine or epilepsy (i.e., prescription, dispensing, and/or consultation visit) in the last 6 months.
- Patient and/or their legally acceptable representative where applicable must sign a participation agreement/Informed Consent Form (ICF) in accordance with local requirements. For patients from 13 to 17 years of age, the survey shall be completed by their parent or caregiver.

HCP inclusion criteria

- HCPs who prescribed and/or dispensed topiramate monotherapy products to WOCBP for the treatment of migraine and/or epilepsy in the last 6 months including GPs, specialists in internal medicine, other specialists managing epilepsy and/or migraine (including neurologists, (general) pediatricians, neuro-pediatricians, psychiatrists), pharmacists, or HCPs who had a consultation with/saw at least one patient with topiramate use for the treatment of migraine and/or epilepsy (OB/GYN, midwives) in the last 6 months.

Participants who meet any of the following criterion will not be eligible for this study:

Patient exclusion criteria

- Patients who may have conflicts of interest with the survey (i.e., patients employed by regulatory bodies or pharmaceutical companies).

HCP exclusion criteria

- HCPs who declare having conflicts of interest with the survey (i.e., HCPs employed by regulatory bodies or pharmaceutical companies).

Variables

Collected through the patient surveys:

- Variables related to the patients treated with topiramate:
    - Patient age range (13-17, 18-30, 31-40, 41-49 years)
    - Length of topiramate treatment (<1 year, 1-5 years, 6-10 years, >10 years)
    - Indication for topiramate treatment (migraine, epilepsy)
- Variables related to patient's awareness of the newly implemented RMMs, including (dependent on the country):
    - Receipt of the Patient Card (Yes/No)
    - Receipt of the Patient Guide (Yes/No)
    - Receipt of the Patient Information Leaflet (Yes/No)
    - Awareness of existence of the Risk Awareness Form (Yes/No)
    - Awareness of warning message on the product package (Yes/No)
    - Having read the Patient Card (Yes/No)
    - Having read the Patient Guide (Yes/No)
    - Having read the Patient Information Leaflet (Yes/No)
    - Having reviewed, completed, and signed the Risk Awareness Form (Yes/No)
- Variables related to patient's knowledge with regards to risks associated with use of topiramate during pregnancy and measures to avoid exposed pregnancies, such as:
    - Understanding the potential risk of using topiramate during pregnancy (Multiple Choice Question [MCQ])
    - Understanding the recommended pregnancy prevention measures during topiramate use (MCQ)
    - Understanding methods of effective contraception (MCQ)
    - Understanding the required actions if pregnancy is detected during topiramate use (true/false questions)
- Variables related to self-reported behavior with regard to the newly implemented RMMs, such as:
    - Having had a pregnancy test before topiramate use (Yes/No)
    - Using effective contraception during topiramate use (MCQ)

Collected through the HCP surveys:

- Variables related to HCPs' participation (targeted, not reachable, contacted, refused to participate, agreed to participate, excluded and reason for exclusion [screening failure vs incomplete survey], completed survey, contact rate, response rate, refusal rate) (Toussi 2021).
- Variables related to HCPs' practice information:
    - Demographic information for HCP:
        - HCP primary specialty (GP/family physician, neuro-pediatrician, specialist in internal medicine, (general) pediatrician, obstetrician/gynecologist (OB/GYN), midwife, pharmacist, psychiatrist, other)
        - Country the HCP practices in (France, Germany, Poland, Spain, Sweden, United Kingdom, other)
        - Duration of practice in primary specialty (<1 year, 1-5 years, 6-10 years, >10 years)
        - Practice setting (office/clinic/practice-based, hospital-based, research-based, other)
        - Year of experience with topiramate (<1 year, 1-5 years, 6-10 years, >10 years)
        - *[excluding pharmacists, midwives, OB/GYNs]* Estimated number of prescriptions of topiramate written to WOCBP aged between ≥13 and ≤49 years for the treatment of epilepsy and/or migraine within the last 6 months
        - *[pharmacists only]* Estimated number of prescriptions of topiramate filled for WOCBP aged between ≥13 and ≤49 years for the treatment of epilepsy and/or migraine within the last 6 months
        - *[excluding pharmacists]* Estimated number of WOCBP aged between ≥13 and ≤49 years receiving topiramate for the treatment of epilepsy and/or migraine and who were seen within the last 6 months
        - *[excluding pharmacists]* Proportion of WOCBP aged between ≥13 and ≤49 years receiving topiramate and who the HCP has seen and/or prescribed topiramate to within the last 6 months by indication (migraine, epilepsy, both, other)
        - *[pharmacists only]* Proportion of WOCBP aged between ≥13 and ≤49 years and for whom HCP has dispensed topiramate within the last 6 months by indication (migraine, epilepsy, both, other)
- Variables related to the HCPs' awareness of the DHPC and EM (dependent on the country):
        - Receipt of and/or access to DHPC (Yes/No/Unsure)
        - Receipt of and/or access to revised Summary of Product Characteristics (SmPC) (Yes/No/Unsure)
        - Receipt of and/or access to HCP Guide (including Risk Awareness Form) (Yes/No/Unsure)
        - Receipt of and/or access to Patient Guide (Yes/No/Unsure)
        - Receipt of and/or access to Patient Card (Yes/No/Unsure)
        - Having read the DHPC (Yes/No/Don't know)
        - Having read the revised SmPC (Yes/No/Don't know)
        - Having read the HCP Guide (Yes/No/Don't know)
        - Having read the Patient Guide (Yes/Nov)
        - Having read the Patient Card (Yes/No/Don't know)

- Variables related to the HCPs' knowledge with respect to the potential risks of topiramate use during pregnancy and measure(s) to be taken to prevent pregnancies among WOCBP exposed to topiramate mono-components products.
    - Understanding the risks associated with topiramate use during pregnancy (MCQ)
    - Understanding the RMMs to avoid prenatal exposure (MCQ)
    - Understanding definition of effective contraception per SmPC
    - Understanding the necessary actions if a patient becomes pregnant during treatment (MCQ)
- Variables related to self-reported behavior with respect to the newly implemented RMMs.
    - Implementation of Risk Awareness Form in practice
    - Counseling for pregnancy testing and prevention
    - Counseling for alternative treatments if necessary

Data Sources

The data source for this survey will be the on-line questionnaires used to survey HCPs involved in prescription, dispensing, and/or consultation of topiramate treatment and WOCBP being treated with topiramate mono-components products at the time of the survey. HCPs and patients (or parents/caregivers) who have passed the screening and who have given consent will move to the survey.

Study Size

The number of completed surveys has been estimated based on feasibility assessments, research questions and objectives. The total sample of 500 patients will be stratified by indication as follows: 170 for epilepsy and 330 for migraine which will achieve a 2-sided 95% confidence interval (CI) of 73.2% - 85.7% and 75.3% - 84.2% for a proportion of 80% knowledge, respectively. The total sample of 1,000 HCPs will be stratified by HCP category (HCPs prescribing/consulting/dispensing) as follows: 345 GPs (including 20 specialists in internal medicine), 345 other specialists managing epilepsy and/or migraine (including neurologists, pediatricians, neuro-pediatricians, psychiatrists), 150 OB/GYN (including 20 midwives), and 160 pharmacists. Samples of 150 HCPs, samples of 160 HCPs, and samples of 345 HCPs will achieve a 2-sided 95% confidence interval (CI) of 72.7% - 86.1%, 73.0% - 85.9%, and 75.4% - 84.1%75.0% - 84.4% for a proportion of 80% knowledge, respectively.

Patient sample targets by indication and HCP sample targets by specialty will be stratified by country based on the number of patients receiving topiramate across the study countries and the approximate number of HCP in each specialty, respectively. In addition, pragmatic adjustments will be applied to allocate sufficient size to less represented strata of the sample and to be closer aligned with country population weight. adjusted pragmatically to ensure a minimal representation in the countries where they are relevant.

Data Analysis

Upon completion of the survey by the required number of respondents, responses will be summarized:

Continuous variables collected in Section 9.3 will be described by their number (of valid responses), mean, standard deviation, and median, first quartile (Q1), third quartile (Q3), minimum and maximum.

Categorical variables will be described as the total number (of valid responses) and percentage per category including 95% CIs.

Within the HCP and patient datasets, a derived variable in the form of a score summarizing all responses at individual participant level will be created for each of the main dimensions of the survey (awareness, knowledge, and behavior). The individual score will be calculated as the proportion of correct responses to awareness questions (having received / having had access and having read the DHPC and EM) and

or has access to the proportion of correct responses among all the sub-questions related to knowledge or behavior. Success for each dimension is defined as a score of at least 80%.

For each dimension, the number and proportion of participants who have a score of at least 80% will be calculated. Success for each dimension is defined as having at least 80% of successful participants.

At a study level (i.e., all dimensions combined), the newly implemented RMMs will be considered satisfactory if the behavior outcome and at least one of the two other outcomes (awareness and/or knowledge) are equal to or above the defined threshold of 80% of successful participants.

Pre-specified sub-group analysis will be conducted by country and indication. Further details will be provided in the statistical analysis plan (SAP).

Milestones

Milestone	**Planned date**
Registration in the HMA-EMA Catalogues of RWD sources and studies	Before start of data collection
Start of data collection	No sooner than 12 months after DHPC and EM distribution in each country
End of data collection	No later than 6 months after start of data collection in each country
Final report of study results	No later than 18 months after PRAC endorsement of the study protocol