ABSTRACT

Title: Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study

Version 2.0, 17 October 2024

Primary Author: Brian Buysse, PhD, Syneos Health, Madrid, Spain

Rationale and Background

In the European Union (EU) and the United Kingdom (UK), topiramate mono-component products are used to treat 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. 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 (SmPCs) and the implementation of additional risk minimization measures in the form of educational materials (health care professional guide and patient guide) under a Pregnancy Prevention Program (PPP). All these actions are henceforth collectively referred to as "newly implemented risk minimization measures (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.

The PRAC requested the MAHs of medicinal products containing topiramate as a mono-component to conduct a drug utilization study to evaluate the effectiveness of the newly implemented RMMs.

The overarching goal of this drug utilization study is to compare the use of topiramate among WOCBP with epilepsy or migraine diagnosis during the pre- and post-implementation periods of the newly implemented RMMs. Trends over time in use of other therapies for epilepsy and migraine prevention will also be described during the same pre- and post-implementation period to contextualize the changes over time to topiramate exposure.

Research Question and Objectives

Research Question

Are the newly implemented RMMs for topiramate associated with change in topiramate use and pregnancy exposure to the drug among WOCBP with epilepsy or migraine diagnosis?

Objectives

The primary objectives are to:

1. Compare the prevalence and incidence rate of use of topiramate and alternative therapies during the pre- and post-implementation periods of the newly implemented topiramate RMMs among WOCBP with epilepsy and/or migraine by indication (epilepsy; migraine; epilepsy and migraine).

2. Describe pregnancy exposure to topiramate during the pre- and post-implementation periods of the newly implemented topiramate RMMs among incident users in WOCBP with epilepsy and/or migraine.

The secondary objectives are to:

1. Describe pregnancy exposure to topiramate during the pre- and post-implementation periods of the newly implemented topiramate RMMs among incident users of topiramate in WOCBP by indication (epilepsy; migraine; epilepsy and migraine; other/unknown).
2. Characterize the incident users of topiramate during the pre- and post-implementation periods of the newly implemented topiramate RMMs among WOCBP by indication (epilepsy; migraine; epilepsy and migraine; other/unknown).

This study will also aim to investigate the following exploratory objective when feasible:

Compare the incidence of topiramate use as first-line treatment during the pre- and post-implementation periods of the newly implemented topiramate RMMs among WOCBP with epilepsy and/or migraine by indication (epilepsy; migraine; epilepsy and migraine).

Study Design

The study design is a pre-post, observational study using data from existing healthcare databases in the EU and the UK.

The pre- and post-implementation periods will be defined as 36 months prior to publication of Bjørk et al. on 31 May 2022 and 36 months after implementation of the new RMMs, respectively.

Study Population

The study population will be drawn from existing healthcare and administrative databases available in four EU countries (France, Germany, Spain, and Sweden) and the UK.

Patients in this study will be WOCBP (≥13 to ≤49 years of age and without prior record of hysterectomy or sterilization) identified in the healthcare database selected for each of the countries. Two cohorts will be created separately for the pre-implementation (Q2 2019-Q2 2022) and post-implementation (Q1 2024-Q1 2027) periods:

- WOCBP Diagnosed Cohort, consisting of WOCBP with epilepsy or migraine and with at least one year of data prior to cohort entry.
- WOCBP Incident User Cohort, consisting of WOCBP with a new prescription or dispensation of topiramate (ie, without topiramate or alternative therapy use for at least 12 months prior to cohort entry).

Variables

Variables to be used during the course of the study time period (prior to cohort-entry, at cohort-entry, and at follow up, as applicable) include: patient and clinical characteristics of interest (age, diagnosis of epilepsy or migraine, comorbidities, hysterectomy/sterilization procedures); prescribing/dispensing of topiramate and other standard-of-care treatments; and healthcare resource utilization.

Outcomes will include the prevalence and incidence of topiramate use in the Diagnosed WOCBP Cohort (by topiramate indication, ie, epilepsy and/or migraine); topiramate treatment initiation during an ongoing pregnancy, and new pregnancies during an ongoing topiramate treatment (in the Incident User Cohort, by topiramate indication). Incident users of topiramate will be characterized. An exploratory outcome is the incidence of topiramate use as first-line treatment in the Diagnosed WOCBP Cohort.

Data Sources

Based on a feasibility assessment on the relevancy and reliability of data sources, the study will be conducted on data obtained from the following databases:

- National Health Data System **(**SNDS**) -** France
- German Pharmacoepidemiological Research Database (GePaRD) - Germany
- Information System for the Development of Research in Primary Care (SIDIAP) - Spain
- National population-based registers - Sweden
- Clinical Practice Research Datalink (CPRD) Aurum - UK

Study Size

Based on feasibility assessment including a combination of direct contact with data access partners and desktop research, the number of WOCBP with epilepsy across data sources ranged between ~7,000 (2018 in Sweden) and ~115,000 (SNDS, 2011-2017) and that of WOCBP with migraine between ~9,500 (Swedish registers, 2022) to more than 3M (SNDS, 2018).

Data Analysis

Data analysis will be performed separately for each database and by indication. All descriptive analyses will be displayed for the pre- and post-implementation periods, overall and by age category and country.

Interrupted time-series analysis is planned for primary objective 1, contingent upon sufficient statistical power. All other study objectives are descriptive.

Continuous variables will be summarized using appropriate statistics for continuous variables (eg, mean, standard deviation (SD), median, range, minimum and maximum). Categorical variables will be summarized using appropriate statistics (eg, number, percentage and 95% Clopper-Pearson confidence intervals).

Milestones

Milestone	**Planned Date**
Start of data collection	2025
End of data collection	2027
Registration in the HMA-EMA Catalogues of RWD sources and studies	This study will be registered after PRAC endorsement of the protocol and before the start of data collection.
Interim report of study results	24 months after PRAC endorsement of the study protocol
Final report of study results	48 months after PRAC endorsement of the study protocol