Janssen-Cilag International

Observational Study Protocol

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

Protocol PCSESPA0008 Update 2
JNJ-17080102-AAA (topiramate)
and topiramate mono-component products of generic companies

Status: Approved
Date: 19 March 2026
Prepared by: Syneos Health
EDMS No.: EDMS-RIM-1159530, 7.0

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PASS INFORMATION

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**
Protocol version identifier:	4.0
Date of last version of the protocol:	12 June 2025
HMA-EMA Catalogues of RWD sources and studies ID:	EUPAS1000000806
Active substance (INN common name):	Topiramate
Pharmaco-therapeutic group (ATC Code):	N03AX11, N02CX12
Medicinal product(s):	JNJ-17080102-AAA and topiramate-mono-component products of generic companies
Product reference:	Refer to ANNEX 5. LIST OF AUTHORIZED TOPIRAMATE MONO-COMPONENT PRODUCTS
Procedure number:	EMEA/H/A-31/1520
Name of Marketing Authorization Holder(s)	Janssen on behalf of the Topiramate Safety Consortium
Joint PASS	Yes
Research question and objectives	*Research question:* What is the impact of the newly implemented risk minimization measures (RMMs) on the knowledge and self-reported behavior of healthcare professionals (HCPs) who prescribe topiramate mono-component products and of patients treated with topiramate mono-component products in the European Union (EU) and United Kingdom (UK)? *Objectives:* To assess the awareness of: • Women of childbearing potential (WOCBP) treated with topiramate mono-component products with respect to the receipt of the Educational Materials (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.

Countries of study	France, Germany, Poland, Spain, Sweden, United Kingdom
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MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen on behalf of the Topiramate Safety Consortium. For a list of all Marketing Authorization Holders, see ANNEX 4.
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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AED	Anti-epileptic Drug
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
DHPC	Direct Healthcare Professional Communication
EM	Educational Material
EMA	European Medicines Agency
EU	European Union
FOIA	Freedom of Information Act
GP	General Practitioner
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HMA	Heads of Medicines Agencies
ICF	Informed Consent Form
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Market Authorization Holder
MCQ	Multiple Choice Questions
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NDD	Neurodevelopmental disorders
OB/GYN	Obstetrician/gynecologist
PASS	Post-Authorization Safety Study
PII	Personal Identifying Information
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
RAF	Risk Assessment Form
RMM	Risk Minimization Measure
RWD	Real-World Data
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TDF	Theoretical Domains Framework
UK	United Kingdom
WOCBP	Women of Childbearing Potential

3. RESPONSIBLE PARTIES

Marketing Authorization Holder:

Janssen on behalf of the Topiramate Safety Consortium. Refer to ANNEX 4 for a list of participating Marketing Authorization Holders.

Contract Research Organization:

Syneos Health

Principal Investigator:

Brian Buysse, PPD, Syneos Health

Recruitment and deployment vendors:

Consumer panels, HCP lists and social media outreach (as needed)

4. 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

Version 4.0, 19 March 2026

Primary Author: PPD MSc, PPD, Syneos Health

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/No)

  - 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	Q4 2027

5. AMENDMENTS AND UPDATES

Document	Country/Territory Affected	Date
Protocol Update 2	All	19 March 2026
Protocol Update 1	All	12 June 2025
Original Protocol	All	18 October 2024

Overall rationale for protocol update 2 (19 March 2026): To revise the study timeline and include administrative amendments (e.g., personnel and contact detail updates, product list updates, and study registration details).

The changes made to the clinical protocol PCSESPA0008 as part of these updates are listed below, including the rationale of each change and a list of all applicable sections.

Update 2 (19 March 2026) – Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
4. ABSTRACT 6. MILESTONES	Revision of the overall study timeline, including delayed initiation of data collection and postponement of the final report submission to PRAC from 16 July 2026 (18 months after protocol endorsement) to Q4 2027	Data collection has been delayed due to the 12-month post-DHPC/EM requirement in each country, variability in Regulatory Authority and Ethics Committee approvals, and extended recruitment timelines, resulting in a revision of the overall study completion and final report submission timeline.
PASS INFORMATION ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS	Addition of the HMA-EMA Catalogue of RWD Sources and Studies registration ID	Study registration completed.
PASS INFORMATION	Change in principal investigator	Personnel change at the CRO.
3. RESPONSIBLE PARTIES	Removal of outdated contact details of the original protocol author and addition of a current CRO contact person	Personnel change at the CRO.
ANNEX 4. LIST AND CONTACT DETAILS OF QPPVs OF REPRESENTED MAHs	Update of QPPV contact details for several MAHs	Personnel changes at MAHs.
ANNEX 5. LIST OF AUTHORIZED TOPIRAMATE MONO-COMPONENT PRODUCTS	Update to the list of topiramate mono-component products	Ensure the list reflects currently marketed topiramate mono-component products in the study countries.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Overall rationale for protocol update 1 (12 June 2025): To revise the protocol's sampling strategy, HCP sampling distribution, and definition of success for awareness dimension.

Update 1 (12 June 2025) – Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
6. MILESTONES	Updated Table 2: Time Schedule of Distribution of DHPC and EM in the Study Countries	Date for France not previously available. Dates for Poland and Sweden corrected.
4. ABSTRACT 9.1. Study Design 9.2.1.3. Participant Selection: Sampling Strategy 9.7.2. Data Collection and Ongoing Data Quality Control 9.8.2. Selection Bias 11. COLLECTION AND REPORTING OF SAFETY DATA AND COMPLAINTS	Updated recruitment vendors to: Consumer panels, commercial HCP lists and social media advertising/outreach (if deemed feasible). Text describing recruitment strategy moved from Section 9.1 to Section 9.2.1.3. Section 9.2.1.3: Updated first paragraph to more accurately describe the sampling strategy.	Names of specific recruitment vendors removed to facilitate the inclusion of a broader participant population, thereby ensuring the identification of sufficient participants and adherence to data collection timelines.
4. ABSTRACT 9.2.1.1. Inclusion Criteria	Included Psychiatrists in the HCP specialties being targeted for the HCP survey.	Psychiatrists are recipients of topiramate educational materials in Poland and Spain.
9.2.1.3. Participant Selection: Sampling Strategy	Entire section updated and sub-sections added for "HCP recruitment" and "Patient recruitment".	More accurately describe the participant selection process, including initial invitation and reminder cadence according to established processes by the different recruitment vendors.
ABSTRACT4. ABSTRACT 9.3. Variables	Updates to variables based on final HCP and Patient surveys (following pretesting).	Changes to HCP and Patient surveys informed by findings from pretesting with a selection of patients and HCPs (completed in April 2025).
9.4.1.1. Pragmatic Total Sample Size Adjustments	Listed the HCP specialties that are targeted in the HCP survey, including relevant countries for each.	Relevance of HCP specialties in each country is guided by local disease management practices.
9.4.1.1. Pragmatic Total Sample Size Adjustments 9.4.2.2. HCP Survey Table 6: 95% CI for Different Assumed Knowledge Rates and Target HCP and Patient Sample Sizes Table 11: Target Sample size by Specialty and Country Table 12: Pragmatic Sample Size Adjustment by Specialty and Country	Updated overall HCP target sample sizes from 330 to 345 GPs (including specialists in internal medicine), from 300 to 345 for other specialists managing epilepsy and/or migraine, from 170 to 150 for OB/GYN (including midwives), and from 170 to 160 for pharmacists. Updated the target sample distribution by country. In countries where it was confirmed that an HCP specialty is not relevant, sample target has been removed and "N/A".	Overall sample targets by HCP type were adjusted because not all HCP specialties are relevant in all countries and therefore a redistribution giving more weight to main HCP specialties (GPs and neurologists) was deemed adequate. Sample distribution of each HCP specialty by country adjusted pragmatically to better reflect its relevance in each country and ensure a minimal representation.
4. ABSTRACT 9.6.2.1. Questionnaire Analysis	Added text clarifying that HCPs who responded that they have not received / have not had access to any of the materials or who are unsure, will	Demographic questions D1 through D7 and awareness question A1 are no longer considered part of the Screener but part of the survey as data for those

Section Number and Name	Description of Change	Brief Rationale
	prematurely end the survey (no screen outs). Updated text to clarify that the individual score for awareness will be calculated as the proportion of correct responses to awareness questions.	prematurely ending the survey will be analyzed and reported. For Awareness dimension, descriptively comparing the group who prematurely ended the survey and the group who completed the survey will generate insight into the effectiveness of distribution of the EMs in the target HCP populations.
ANNEX 4. LIST AND CONTACT DETAILS OF QPPVs OF REPRESENTED MAHs	Some contact details have been updated.	
ANNEX 5. LIST OF AUTHORIZED TOPIRAMATE MONO-COMPONENT PRODUCTS	Details for Poland were missing.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

6. MILESTONES

The planned dates for key milestones in this study are outlined in Table 1.

Table 1: Study 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	Q4 2027

The time schedule of distribution of DHPC and EM in each study country is summarized in Table 2.

Table 2: Time Schedule of Distribution of DHPC and EM in the Study Countries

Type of Material	France	Germany	Poland	Spain	Sweden	UK
Distribution date of DHPC	23 October 2023	02 November 2023	02 November 2023	02 November 2023	21 February 2024	27/28 June 2024
Distribution date of educational material (HCP Guide, Patient Guide, RAF, Patient Card)	13 December 2024	02 November 2023	17 April 2024	20 June 2024	21 February 2024	27/28 June 2024

Abbreviations: DHPC, direct healthcare professional communication; EM, educational material; HCP, healthcare professional; RAF, risk awareness form; UK, United Kingdom.

7. RATIONALE AND BACKGROUND

7.1. Background

Epilepsy is a chronic disorder that disrupts nerve cell activity in the brain and affects around 50 million people worldwide, making it one of the most common neurological diseases globally. Seizure episodes are a result of excessive electrical discharges in a group of brain cells (WHO 2023). Migraine is one of the most common neurological disorders that affects 12% of the global population with a high prevalence and morbidity, especially among young adults and females. Migraine is associated with a wide range of comorbidities, which range from stress and sleep disturbances to suicide (Amiri 2022). According to the Epilepsy Foundation, people with epilepsy are twice as likely to have migraine headaches (Epilepsy Foundation 2023). Migraine concomitant with epilepsy increases the risk of the patient developing drug-resistant epilepsy, depression, and anxiety disorders, as well as significantly decreases the quality of life (Czapińska-Ciepiela 2018).

7.2. Current Treatments

Several medications can be used to treat epilepsy, referred to as anti-epileptic drugs (AEDs) or anticonvulsants. These medications work by reducing bursts of electrical activity in a patient's brain and restoring the normal balance of nerve activity (NHS 2023). Several pharmacotherapies are approved for migraine prevention (Lew 2023).

Topiramate was initially approved in 1995 in the UK as adjunctive treatment of partial-onset seizures in adult epilepsy patients (Naegel 2010). Topiramate is currently approved (TOPAMAX SmPC 2024):

- as monotherapy in individuals aged six years and above with partial seizures with or without secondary generalized seizures, and primary generalized tonic-clonic seizures.
- as adjunctive therapy in individuals aged two years and above with partial-onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.
- in adults for prophylaxis of migraine headache after careful evaluation of possible alternative treatment options.

Topiramate is associated with increased risk of congenital malformations, particularly oral clefts, if used in pregnancy, (Hunt 2008; Tennis 2015; Hernandez-Diaz 2018; Blotière 2019). Other potential adverse effects associated with perinatal exposure of topiramate are fetal growth restriction, including low birth weight and small for gestational age (Hernandez-Diaz 2014; Van Marter 2021). Due to these established concerns, topiramate has already been contraindicated for migraine prophylaxis in pregnancy and in women of childbearing potential (WOCBP) if a highly effective method of contraception is not used. Per the Topamax Summary of Product Characteristics (SmPC) (TOPAMAX SmPC 2024):

SmPC Section 4.4 *Special warnings and precautions for use*

Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed, and a highly effective contraceptive method advised (see Section 4.5). The patient should be fully informed of the risks related to the use of topiramate during pregnancy (see Sections 4.3 and 4.6)

SmPC Section 4.3 *Contraindications*:

Migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

SmPC Section 4.6 *Indication migraine prophylaxis*

Topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see Sections 4.3 and 4.5)

7.3. Overall Rationale for the Study

In 2022, the Nordic register-based study of anti-epileptic drugs in pregnancy (SCAN-AED) found that topiramate exposure during pregnancy was associated with neurodevelopmental disorders (NDDs) in children (Bjørk 2022).

Following the publication of the Bjørk 2022 study, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended updates to the SmPC and patient information leaflet (PIL) and requested additional risk minimization measures (RMMs), to reduce drug utilization by WOCBP in all approved indications unless no suitable alternative treatment is available and appropriate contraception is used. All these actions are henceforth collectively referred to as “newly implemented RMMs”. The newly implemented RMMs required by PRAC add to the existing topiramate RMMs (topiramate mono-component products must not be used to prevent migraine during pregnancy and patients who can become pregnant must use effective birth control when using topiramate.) For patients using topiramate for the treatment of epilepsy, the medicine should not be used during pregnancy unless there is no suitable treatment available. The existing and newly implemented RMMs are listed in ANNEX 3.

To evaluate the knowledge and adherence to the RMMs, PRAC requested Healthcare Professional (HCP) and patient surveys be conducted to assess the effectiveness of newly implemented RMMs (i.e., updated label warnings and contraindications, HCP guide including risk awareness form, patient guide, patient card, outer package warnings) in raising the awareness and understanding of this target population with respect to the safe use of topiramate.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. 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?

8.2. 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 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.

9. RESEARCH METHODS

9.1. Study Design

This is a cross-sectional, multinational, and non-interventional survey conducted among 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) and WOCBP patients exposed to topiramate mono-component products in six European countries (five EU member states and the UK).

9.1.1. Study Countries

A total of 6 countries (France, Germany, Poland, Spain, Sweden, and the UK) were chosen based on the following criteria:

- Representativeness in term of largest topiramate sales in Europe (Table 3)
- Representativeness in term of small and large countries
- Representativeness in term of different health care systems
- Representativeness in term of geographical spread across Europe (Western, Eastern, Northern and Southern regions)

Considering this requirement for diverse geographic representation of European countries, an additional criterion of selection has been applied based on the use of topiramate in European countries. The unit volume of sales of topiramate was used as a proxy to assess the prevalence of patients or eligible HCPs having experience with topiramate (Table 3).

Table 3: Proportion of Topiramate Utilization in 2023 in the European Market

Country	Relative proportion*
France	6.7%
Germany	7.6%
Poland	3.1%
Spain	17.7%
Sweden	1.0%
UK	18.0%

Source: IQVIA MIDAS®; MIDAS Audited Sales Unit Volume; Accessed on 23 September 2024.

The UK is included to fulfill a concurrent request from the Medicines and Healthcare products Regulatory Agency (MHRA) to assess the effectiveness of RMMs in that region. One harmonized evidence generation program that includes a selection of countries across the EU and the UK will enable to more efficiently address both EMA and MHRA regulatory requests by leveraging a single study infrastructure.

9.1.2. Approaches for Increasing Response Rates

To ensure that the invitation and survey are comprehensible, all outreach will be conducted in the local language of each country. To increase the response rate among HCPs and patients, a

compensation fee will be proposed for their participation in the survey. A preset fair market value (FMV) compensation will be provided to participants for their time and effort.

9.2. Setting

This study will be conducted among WOCBP and HCPs through on-line questionnaires. The survey (and other participant facing documents) will be in the local language. 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 EMs' effectiveness.

9.2.1. Patient and HCP Selection Criteria

9.2.1.1. Inclusion Criteria

The target population of the survey will be composed of WOCBP who are treated with topiramate and HCPs grouped into three categories: 1) those who prescribe topiramate, 2) those who dispense topiramate, and 3) those who consult with or see patients receiving topiramate, in the targeted countries.

Each participant in their respective category must satisfy the following criteria to be eligible for data collection in this study:

Patients

- WOCBP (≥13 and ≤49 years of age) and being treated with topiramate mono-components products 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 six months.
- Patient and/or their legally acceptable representative where applicable must sign an 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.

HCPs

- Prescribers: HCPs at office-based practices and/or hospitals including GPs, specialists in internal medicine, other specialists managing epilepsy and/or migraine (neurologists, (general) pediatricians, neuro-pediatricians, psychiatrists) who prescribed topiramate mono-component products to WOCBP for the treatment of migraine and/or epilepsy in the last 6 months.
- OB/GYN (including midwives): Obstetricians/gynecologists or midwives who had a consultation with/saw at least one WOCBP treated with topiramate mono-components products for the treatment of migraine and/or epilepsy in the last six months.
- Pharmacists: Pharmacists (including retail and hospital pharmacists) who dispensed topiramate mono-components products to WOCBP for the treatment of migraine and/or epilepsy in the last six months.

9.2.1.2. Exclusion Criteria

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

Patients

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

HCPs

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

9.2.1.3. Participant Selection: Sampling Strategy

HCPs and patients will be recruited via multiple sources:

1. third-party consumer panel(s),
2. commercial HCP lists (such as Veeva OpenData), and
3. social media advertising/outreach (if deemed feasible). The social media strategy would be conducted by a vetted and approved recruitment vendor operating an actively managed on-line forum.

Surveys will not be administered through the social media strategy. Consumer panel vendors provide access to patients and verified HCPs (i.e., who have pre-consented to be contacted for research surveys) across the six target countries. HCP lists will enable outreach to and recruitment of HCPs who are not included in the consumer panel(s) and allow the recruitment of additional patients and parents/caregivers of adolescents (≥13 and ≤17 years of age) via HCP referrals. Feasibility across combined vendors has confirmed access to the required number of participants who meet the inclusion criteria, as detailed in sample stratification in Table 8 and Table 12. Patient samples may be supplemented via social media outreach only if target quota cannot be achieved via the other recruitment sources, and if deemed feasible.

To minimize selection bias, a list of potential participants (HCPs or patients) will be generated via random sampling method for the first wave of outreach. For patients (or parents/caregivers) being recruited via HCP referrals, HCPs will be asked to approach patients (or parents/caregivers) sequentially to mitigate potential selection bias.

Potential participants (HCPs, patients, parents/caregivers) will have access to an on-line consent form followed by a screening questionnaire to determine their eligibility to participate. A potential participant who meets the inclusion criteria and who has provided all necessary consents will move to the on-line study survey if the quota for their stratum has not been met. Throughout this process, data will be collected to show number of invitations sent, number of screen outs (total and by reason), and number of screen ins who did not provide final consents.

The HCP and patient recruitment process including cadence of reminders differs by recruitment vendor and is based on their established algorithms aiming to achieve most effective invitation uptake. This cadence is a factor in feasibility calculations and is designed to optimize recruitment.

HCP Recruitment

The **primary HCP recruitment process**, including reminder cadence, is as follows.

An initial invitation will be sent out by email and will be available on the panelist's individual dashboard. Day 0 is set as the date the invitation link is available. Up to three reminders will be sent by email:

- The first reminder is sent on Day 2 following the initial invitation.
- The second reminder is sent on Day 4 following the initial invitation.
- The third and final reminder is sent on Day 7 following the initial invitation.
- The potential participant is considered lost to follow up if they did not initiate the survey by Day 14 post Day 0 (day of initial invitation).

Partial responders are participants who have initiated but have not completed the survey. Up to three reminders will be sent by email to remind participants of their incomplete response and encouraging non-completers to finalize the survey. The Start Day is the day the participant started the survey. Reminder cadence is as follows:

- The first reminder is sent on "Start Day" + 3 days.
- The second reminder is sent on "Start Day" + 10 days.
- The third reminder is sent on "Start Day" + 14 days.
- The participant is considered lost to follow up if they have not completed the survey by "Start Day" + 21 days. The participant will then be replaced via additional recruitment.
- Surveys completed post-Day 21 will be considered if quota space is available.

If additional HCP recruitment is needed, the **secondary recruitment process** will be initiated. The secondary HCP recruitment process has a single cadence of invitation and completion reminders with the aim of delivering completed surveys within 21 days from receipt of the study invitation.

Initial invitations to HCPs who are verified panel members will be sent in a daily email summary of all available projects for their participation. The invitation to the Topiramate aRMM survey will be available on the panelist's individual dashboard. Day 0 is set as the date the invitation link is available. Potential participants who have not clicked on the initial invitation link, have not completed consent, have not completed the screener, have not initiated the survey or are partial completers will receive up to 5 reminders in total. Reminder cadence is as follows:

- The first reminder is sent on Day Three.
- The second reminder is sent on Day Seven.
- The third reminder is sent on Day 10.
- The fourth reminder is sent on Day 14.

- The fifth and final reminder is sent on Day 17.
- The participant is considered lost to follow-up if they have not initiated or completed the survey by Day 21. The participant will then be replaced via additional recruitment.
- Surveys that are completed post-Day 21 will be considered if quota space is available.

Commercial HCP lists may be used to supplement HCP recruitment. HCPs identified for inclusion will be cross checked against the recruitment vendor's invitation lists to prevent repeat invitations. HCPs who are deemed new will receive an invitation to participate from the recruitment vendor and follow the recruitment vendor's invitation and reminder cadence.

Patient Recruitment

The **primary patient recruitment** process has a single sequence of invitation and completion reminders with the aim of delivering completed surveys within 21 days from receipt of the study invitation.

Initial invitations to patients who are panel members will be sent in a daily email summary of all available projects for their participation. The invitation to the Topiramate aRMM survey will be available on the panelist's individual dashboard. Day 0 is set as the date the invitation link is available. Potential participants who have not clicked on the initial invitation link, have not completed consent, have not completed the screener, have not initiated the survey or are partial completers will receive up to 5 reminders in total. Reminder cadence is as follows:

- The first reminder is sent on Day 3.
- The second reminder is sent on Day 7.
- The third reminder is sent on Day 10.
- The fourth reminder is sent on Day 14.
- The fifth and final reminder is sent on Day 17.
- The participant is considered lost to follow-up if they have not initiated or completed the survey by Day 21. The participant will then be replaced via additional recruitment.
- Surveys that are completed post-Day 21 will be considered if quota space is available.

Supplementary recruitment sources may be employed in case of recruitment delays:

- Commercial HCP lists may be used to identify HCPs who are willing and able to refer patients (or parents/caregivers). HCPs will be invited to refer patients who meet the inclusion criteria. Patients who are interested in joining the study will then be managed by a recruitment partner inclusive of email outreach to invite the patient to join the panel and presentation of the study opportunity.
- Social media outreach may be used via advertising conducted by a recruitment vendor with actively managed on-line discussion forums. A targeted pre-screener will be employed to confirm use of topiramate for epilepsy and/or migraine. An invitation to participate in the survey will be sent to potential participants who meet the prescreen eligibility criteria. Social media recruitment reminder cadence is as follows:

- The first reminder is sent on Day 2 post the initial invitation.
- The second reminder is sent on Day 4 post the initial invitation.
- The third reminder is sent on Day 7 post the initial invitation.

Recruitment will be monitored continuously, and for a given stratum will cease when the target sample is met. Recruitment in a country will cease six months post initiation of field work.

HCP and Patient Recruitment Follow-up Process

For each potential participant or partial completer, the number of times the HCP or patient/parent/caregiver was contacted, as well as the date and time when they completed the on-line survey will be recorded.

If recruitment of HCPs or patients (or parents/caregivers) via the primary consumer panel has been exhausted in any stratum or shows recruitment delays, recruitment via supplementary recruitment sources will be initiated: commercial HCP lists and/or, if deemed feasible, social media outreach (for patients). If recruitment of HCPs, patients (or parents/caregivers) has been exhausted in any stratum, recruitment in this stratum will be prematurely ended, and the sample size targets for the other countries will be readjusted to achieve the total target across all countries.

9.2.2. Duration of Study Period(s) and Follow-Up

This will be a survey that patients and HCPs will complete only once, in their own time. Questionnaire completion time has been estimated to take 10-15 minutes each.

The data collection period in each country (i.e., fieldwork) will last until no later than 6 months after start of data collection, and initiation will be staggered by country dependent on the timing of the distribution of the EMs containing the newly implemented RMMs (i.e., fieldwork to start no sooner than 12 months after their distribution).

9.3. Variables

Questionnaires are designed, tested, and validated through pilot testing to evaluate the clarity and understanding of the questions. The Theoretical Domains Framework (TDF) (Francis 2012) is applied when designing the surveys to elicit measures of awareness and knowledge of EMs and of behavior, in line with the newly implemented RMMs and SmPC/PIL. Careful consideration has been required to design appropriate survey questions that allow assessment of patient and HCP awareness and understanding of the Key Messages included.

A list of suggested topiramate Key Messages is provided in Table 4. These Key Messages feature in the topiramate EMs and have been formulated to aid questionnaire development by directly addressing the objectives of the survey as outlined in Section 8.

Table 4: List of Key Messages to be Tested Through the Questionnaires

Topiramate Key Message to Be Assessed	Materials Where Messaging Is Contained
Patient survey	

The patient has received a copy of the patient guide and/or patient card and has reviewed, completed, and signed the risk awareness form with her physician.	Risk Awareness Form/ Patient Guide/ Patient Card
The patient understands/knows why she needs to be treated with topiramate rather than another alternative.	Risk Awareness Form/ Patient Guide
The patient had a visit where her physician checked the need for topiramate treatment and to consider alternative treatment options.	Patient Guide
Children whose mothers took topiramate during pregnancy: a. have a higher risk of birth defects, b. have a higher risk of being smaller and weighing less than expected at birth, c. may have a higher risk of neurodevelopmental problems.	Risk Awareness Form/ Patient Guide
Untreated epilepsy can also put an epilepsy patient and the unborn child at risk.	Risk Awareness Form/ Patient Guide
A negative pregnancy test should be obtained before treatment with topiramate is started.	Risk Awareness Form/ Patient Guide
Parents/caregivers need to inform the prescribing physician of topiramate when the minor under his/her care experiences menarche (the first occurrence of their period). Tested via question specifically for parents/caregivers (of adolescents receiving topiramate).	Risk Awareness Form/ Patient Guide
Patient needs to consult her physician if there's a plan to become pregnant, to evaluate if it is possible to switch to alternative treatment before the patient stops contraception.	Risk Awareness Form/ Patient Guide/ Patient Card
Highly effective contraception without interruption during the entire duration of topiramate's treatment and for four weeks after stopping treatment must be used by the patient.	Risk Awareness Form/ Patient Guide/ Patient Card
Patient should promptly talk to her physician if she thinks she may be pregnant.	Risk Awareness Form/ Patient Guide/ Patient Card
In case of pregnancy: a. a migraine patient needs to stop treatment straight away, b. an epilepsy patient should not stop treatment until she has discussed this with her physician.	Patient Guide/ Patient Card
In case of pregnancy, the patient needs appropriate monitoring of her unborn child.	Risk Awareness Form/ Patient Guide
HCP Survey	
Physician should be visited at least once a year to review whether topiramate remains the best treatment option.	Risk Awareness Form/ HCP Guide/ Patient Card

Topiramate can cause major congenital malformations and fetal growth restriction when used during pregnancy. Recent data suggest a possibly increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders, intellectual disability, and attention deficit hyperactivity disorder (ADHD) following topiramate use during pregnancy.	HCP guide/ DHPC
New contraindications apply for the treatment of epilepsy: a. In pregnancy, unless there is no suitable alternative treatment. b. In women of childbearing potential not using highly effective contraception. The only exception is a woman for whom there is no suitable alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy.	HCP guide/ DHPC
Topiramate for prophylaxis of migraine is contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception.	HCP guide/ DHPC/ Patient Card
Treatment of female children [country dependent; different indications approved] and WOCBP should be initiated and supervised by a physician experienced in the management of epilepsy or migraine.	HCP guide/ DHPC
The need for treatment should be reassessed at least annually.	HCP guide/ DHPC
HCPs should complete the Risk Awareness Form with their patient at initiation, at annual review, when a patient plans a pregnancy or has become pregnant.	HCP guide/ DHPC
Patients must be fully informed about the potential risks related to the use of topiramate during pregnancy.	HCP guide/ DHPC
Due to a potential interaction, women using systemic hormonal contraceptives should be advised to also use a barrier method.	HCP guide/ DHPC
Pregnancy testing should be performed before initiating treatment.	HCP guide/ DHPC
For women of childbearing potential currently using topiramate, the treatment should be re-evaluated to confirm that the newly implemented RMMs are adhered to.	HCP guide/ DHPC

The following variables will be collected through the **patient survey**:

- 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 receipt and reading (i.e., awareness) of EM (options dependent on country):
  - Receipt of the Patient Card (Yes/No)
  - Receipt of the Patient Guide (Yes/No)
  - Receipt of the Patient Information Leaflet (Yes/No)
  - Receipt 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 respect to the newly implemented RMMs (options for "having read" dependent on country):
  - Having had a pregnancy test before topiramate use (Yes/No)
  - Using effective contraception during topiramate use (MCQ)

The following variables are collected through the **HCP surveys**:

- Variables related to HCP participation (targeted, not reachable, contacted, refuse to participate, agree 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 HCP practice information:
  - Demographic information for HCP:
    - HCP primary specialty (GP/family physician, neurologist, neuro-pediatrician, specialist in internal medicine, (general) pediatrician, obstetrician/gynecologist (OB/GYN), midwife, pharmacist, psychiatrist, other)
    - Country the HCP practices in the majority of their time (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)
  - Years 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 HCP's receipt and reading (i.e., awareness) of the DHPC and EM (options dependent on 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/No/Don't know)
  - Having read the Patient Card (Yes/No/Don't know)
- Variables related to the HCP 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 (options for "having read" dependent on country):
  - Implementation of risk awareness form in practice
  - Counseling for pregnancy testing and prevention
  - Counseling for alternative treatments if necessary

9.3.1. Criteria for Success

Previous studies on the impact of newly implemented RMMs on HCP knowledge and behavior have had mixed results, with knowledge and behavior adoption scores commonly between 60-80% across various RMM programs (Crijns 2013; Madison 2019; Schnetzler 2022; Toussi 2021). Therefore, neither the current state of risk minimization science, nor Module XVI of Good Pharmacovigilance Practices (GVP) revision 3 support a clear criterion for success (Good pharmacovigilance practices, 2024). As such, a subjective threshold measure of 80% for composite HCP and patient knowledge and behavior adoption scores is proposed.

9.4. Study Size

9.4.1. Sample Size Calculation

The number of completed HCP and patient surveys has been estimated based on feasibility assessments, research questions and objectives.

To calculate the target sample sizes required for a proportion of interest (i.e., of HCPs and patients being aware, knowledgeable and adherent to RMMs), the normal approximation to the binomial distribution is used:

$$n = \frac{P \cdot (1 - P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, e is one half the desired width of the CI, and Z_1–$\alpha/2$ is the standard normal Z value corresponding to a cumulative probability of $1 - \alpha/2$ (e.g., if $\alpha = 0.05$ then $Z = 1.96$).

Table 5 provides sample sizes for different levels of "proportion of interest" and different margins of error for 95% CI. The proportions of interest here are the proportions (i.e., success threshold) of HCPs and patients being aware, knowledgeable and adherent to RMMs. Given the lack of a clear criterion for such a threshold, a proportion of 80% is deemed reasonable for both populations. For an expected minimum level of precision of 5% for a population, the target sample size is 246.

Table 5: Margin of Error for 95% CI Based on Various Sample Sizes and Proportions of Interest

	Margin of error for 95% CI (precision)			
Proportion of Interest *	**7%**	**5%**	**4%**	**3%**
50%	196	384	600	1,067
60%	189	369	577	1025
70%	165	323	504	896
80%	126	246	385	683
90%	71	139	216	384

*The proportions of interest are the proportions (i.e., success threshold) of HCPs and patients being aware, knowledgeable and adherent to RMMs. Assuming a proportion of 80% for both populations and an expected minimum level of precision is 5%, the target sample per indication would be 246.

9.4.1.1. Pragmatic Total Sample Size Adjustments

For the patient survey, both indications (migraine and epilepsy) are sub-populations of equal interest.

Topiramate 2023 sales data (IQVIA MIDAS; Accessed on 12 July 2024) suggest a small proportion of patients are being treated for epilepsy (between 1-6% dependent on country) and of those nearly 53% are female (TriNetX; Accessed 26 July 2024). Therefore, the target sample size of 246 is adjusted pragmatically as follows, targeting a total sample of 500 patients:

- Epilepsy: 170 patients, enabling precision levels ≤7% for a proportion of interest of 80%
- Migraine: 330 patients, enabling precision level of ≤5% for a proportion of interest of 80%

For the HCP survey, the relevance of HCP specialties in each country is guided by local disease management practices and consequently the population to whom the topiramate educational materials have been distributed. The following HCP specialties will be targeted in the HCP survey:

- GPs: all countries
- Specialists internal medicine: Germany, Spain, Sweden
- Neurologists: all countries
- Neuro-pediatricians: Germany, Poland, Sweden
- Psychiatrists: Poland, Spain
- (General) pediatricians: all countries, except Poland and UK
- Midwives: all countries, except Sweden and UK
- Pharmacists: all countries, except Sweden

The aim is to achieve acceptable levels of precision for HCPs prescribing/consulting/dispensing and pragmatic adjustments are applied as follows:

- GPs/specialists in internal medicine: 345, enabling precision level of ≤5% for a proportion of interest of 80%. This group will be composed of 325 GPs and a desired sample of 20 specialists in internal medicine based on the assumption that in some countries (e.g., Germany) this HCP category can act as GPs.

- Other specialists managing epilepsy and/or migraine: 345, enabling precision level of ≤5% for a proportion of interest of 80%. This group will be composed of 295 neurologists (including neuro-pediatricians), a desired sample of 20 psychiatrists, and a desired sample of 30 (general) pediatricians based on the assumption that among all patients treated with topiramate, the age category "17 years and younger" represents between 0-10% for epilepsy and between 1-3% for migraine (source France and Germany: IQVIA Disease Analyzer, 2021 calendar year; source UK: CPRD, 2021 calendar year).
- OB/GYN/midwives: 150, enabling precision level of ≤7% for a proportion of interest of 80%. This group will be composed of 130 GYN/OBS and a desired sample of 20 midwives.
- Pharmacists: 160, enabling precision level of ≤7% for a proportion of interest of 80%.

Target population sizes with different expected composite knowledge rates (50%, 80%, and 100%) will achieve two-sided CIs as detailed in Table 6 below.

Table 6: 95% CI for Different Assumed Knowledge Rates and Target HCP and Patient Sample Sizes

Target Sample Size	Composite Knowledge Rate	95% CIs *
20	50%	27.2% - 72.8%
30	50%	31.3% - 68.7%
130	50%	41.1% - 58.9%
150	50%	41.7% - 58.3%
160	50%	42.0% - 58.0%
250	50%	43.6% - 56.4%
295	50%	44.3% - 56.0%
345	50%	44.5% - 55.3%
500	50%	45.5% - 54.5%
750	50%	46.4% - 53.6%
1000	50%	46.9% - 53.1%
20	80%	56.3% - 94.3%
30	80%	61.4% - 92.3%
130	80%	72.1% - 86.5%
150	80%	72.7% - 86.1%
160	80%	73.0% - 85.9%
250	80%	74.5% - 84.8%
295	80%	75.0% - 84.4%
345	80%	75.4% - 84.1%
500	80%	76.2% - 83.4%
750	80%	77.0% - 82.8%
1000	80%	77.4% - 82.4%
20	100%	83.2% - 100%
30	100%	88.4% - 100%
130	100%	97.2% - 100%
150	100%	97.6% - 100%
160	100%	97.7% - 100%
250	100%	98.5% - 100%
295	100%	98.8% - 100%
345	100%	98.9% - 100%
500	100%	99.3% - 100%
750	100%	99.5% - 100%
1000	100%	99.6% - 100%

*Clopper-Pearson (exact) 2-sided CIs (calculations were made using PASS 15.0 software).

9.4.2. Sampling Distribution by Country

9.4.2.1. Patient Survey

The total target sample of patients, by indication, will be stratified by country based on the number of patients being prescribed topiramate by indication (Table 7).

Table 7: Number and Proportion of Topiramate Patients in 2023

Country	Epilepsy N(%)	Migraine N(%)	Epilepsy and Migraine
France	16,173 (13%)	268,394 (8%)	284,567 (8%)
Germany	24,840 (20%)	678,165 (21%)	703,005 (21%)
Poland	11,713 (9%)	288,287 (9%)	300,000 (9%)
Spain	13,143 (10%)	933,982 (29%)	947,125 (28%)
Sweden	2,194 (2%)	58,825 (2%)	61,019 (2%)
UK	57,525 (46%)	1,023,587 (31%)	1,081,112 (32%)
TOTAL	**125,588**	**3,251,240**	**3,376,828**

Source: IQVIA MIDAS®; Drug-Treated Patients; Accessed 12 July 2024.
Source Poland: 300,000 unique patients receiving topiramate provided by Steering Committee and % distribution by indication calculated using the average from the other countries (J&J Poland, estimate (2024)).

However, due to the difference in country size, such a sample distribution is not feasible as it yields a too small sample target in a smaller country such as Sweden. Also, differences in country prescribing practices also impact the distribution (e.g., high prescribing in the UK increases its proportion in the overall population for both indications). A pragmatic adjustment of target samples by country will therefore be proposed to allocate sufficient size to the less represented strata of the sample and reduce the weight of the UK specifically for the epilepsy group (Table 8).

Table 8: Target sample Size by Indication and by Country and Pragmatic Sample Size Adjustment

	Based on number of topiramate patients (2023 calendar year)		Pragmatic adjustment	
Country	**Target sample size epilepsy**	**Target sample size migraine**	**Target sample size epilepsy**	**Target sample size migraine**
France	22	27	30	50
Germany	34	69	40	75
Poland	16	29	20	35
Spain	18	95	25	65
Sweden	3	6	10	20
UK	78	104	45	85
TOTAL	**170**	**330**	**170**	**330**

Source: Calculated using data in Table 7.

9.4.2.2. HCP Survey

For each of the main HCP specialties, the total target sample of HCPs will be stratified by country based on the number of HCPs in each country (Table 9 and Table 10). A limitation of this method is that these distributions do not reflect country-specific differences in prescribing/dispensing patterns across countries (e.g., extreme example where topiramate is not prescribed by a given HCP specialty).

Table 9: Number of HCPs by Specialty and Country

Country	GPs	Neurologists	Pediatricians	OB/GYNs	Pharmacists
France	93,726[1]	2,599[3]	8,556[1]	8,031[1]	65,252[11]
Germany	86,107[1]	6,751[4]	14,924[1]	21,688[1]	55,910[11]
Poland	33,409[1]	3,003[5]	6,500[1]	6,649[1]	27,454[11]
Spain	44,762[1]	2,062[6]	13,133[1]	6,166[1]	59,440[11]
Sweden	6,305[1]	443[7]	1,079[1]	1,408[1]	16,989[11]
UK	54,759[2]	1,805[8]	10,058[9]	7,943[10]	80,000[12]
TOTAL	**319,068**	**17,445**	**55,069**	**51,885**	**307,012**

1. European Union (EU) statistics on physicians - Data extracted in July 2023. (Eurostat, 2024)
2. 2022 estimate of 0.81 per 1,000. (OECD Data Explorer, 2024)
3. 2017 estimate of 3.8 per 100,000. (World Health Organization, The Global Health Observatory, France, 2024)
4. 2015 estimate of 8.09 per 100,000. (EuropeinNumbers Germany, 2024)
5. 2015 estimate of 8.20 per 100,000. (EuropeinNumbers Poland, 2024)
6. 2015 estimate of 5.85 per 100,000. (EuropeinNumbers Spain, 2024)
7. 2017 estimate of 4.2 per 100,000. (World Health Organization, The Global Health Observatory, Sweden, 2024)
8. 2016 estimate of 2.67 per 100,000. (EuropeinNumbers United Kingdom neurologists, 2024)
9. 2018 estimate of 16.09 per 100,000. (EuropeinNumbers United Kingdom pediatric doctors, 2024)
10. 2018 estimate of 11.75 per 100,000. (EuropeinNumbers United Kingdom gynecologists/obstetricians, 2024)
11. 2021 estimates per 10,000 population. (World Health Organization, National Health Workforce Accounts Data Portal (NHWA), 2024).
12. Annual number of pharmacists in the United Kingdom (UK) from 2010 to 2023. (Statista. Health, Pharma & Medtech, 2024)

Table 10: Proportion of HCPs by Specialty and Country

Country	GPs	Neurologists	Pediatricians	OB/GYNs	Pharmacists
France	29%	15%	16%	15%	21%
Germany	27%	39%	27%	42%	18%
Poland	10%	17%	12%	13%	9%
Spain	14%	16%	24%	12%	20%
Sweden	2%	3%	2%	3%	6%
UK	17%	10%	20%	15%	26%
TOTAL	**100%**	**100%**	**100%**	**100%**	**100%**

Source: Calculated using data in Table 9.

Like for patients, due to differences in country size, such a sample distribution is not feasible as it yields sample targets that are too small in smaller countries such as Sweden. Also, differences in country health systems impact the distribution (e.g., high number of neurologists in Poland) (Table 11).

Table 11: Target Sample size by Specialty and Country

Country	GPs	Neurologists	Pediatricians	OB/GYNs	Pharmacists
France	94	44	5	20	34
Germany	88	115	8	55	29
Poland	33	50	4	17	14
Spain	46	47	7	16	32
Sweden	7	9	1	4	10
UK	55	30	6	20	42

TOTAL	**325**	**295**	**30**	**130**	**160**

Source: Calculated using data in Table 10.

A pragmatic adjustment of target samples by country is therefore proposed to allocate more realistic samples sizes to the less represented strata of the sample and to be closer aligned with country population weight (Table 12). For the HCP specialties that are deemed less critical because they are not relevant in several countries and/or expected to play a lesser role in the management of patients treated with topiramate (specialists in internal medicine, (general) pediatricians, neuro-pediatricians, psychiatrists, and midwives), the overall sample targets have been adjusted pragmatically to ensure a minimal representation in the countries where they are relevant.

Table 12: Pragmatic Sample Size Adjustment by Specialty and Country

Country	GPs	Specialists IM	Neurologists + neuro-pediatricians	Psychiatrists	Pediatricians	OB/GYNs	Midwives	Pharmacists	Total
France	70	N/A	60	N/A	10	40	5	35	235
Germany	70	10	65 + 5	N/A	10	45	5	40	245
Poland	35	N/A	40 + 5	15	N/A	N/A	5	20	125
Spain	40	5	30	5	5	35	5	25	155
Sweden	25	5	13 + 2	N/A	5	10	N/A	N/A	75
UK	85	N/A	75	N/A	N/A	N/A	N/A	40	215
TOTAL	**325**	**20**	**283 + 12**	**20**	**30**	**130**	**20**	**160**	**1,000**
	345		**345**			**150**			

Source: Calculated using data in Table 11.

For both the patient and HCP surveys, the aim is to preserve the strata by indication/HCP specialty and country as much as possible, and the expectation based on prior feasibility is that this is achievable with the combined recruitment sources. In case recruitment of patients or HCPs in any stratum in a country is exhausted, the sample size targets for the other countries will be readjusted to achieve the total sample size targets by indication or HCP specialty (see Section 9.2.1.3.).

9.5. Data Management

Syneos Health, via its recruitment vendors, will perform rigorous ‘real-time’ checks to ensure that the data collected are valid and of high quality. These checks will involve:

- Reviewing the length of time participants take to complete sections of the survey, as well as total survey length.
- Looking at patterned responses to questions

Individuals are increasingly contacted to participate in web or phone surveys. The overall response rate of participation remains low according to international studies (Kellerman 2001; Curtin 2005; Holbrook 2007; VanGeest 2007). To increase the response rate, the following considerations will be applied to this survey:

- Each questionnaire completion will take 10-15 minutes.
- FMV payment will be offered for time spent participating in the survey.

9.6. Data Analysis

A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the statistical analysis plan (SAP). The final SAP will include table shells to be populated for the clinical study report.

The statistical analysis will be conducted using the SAS® software Linux release 8.3 (SAS Institute, North Carolina, USA).

9.6.1. General Considerations

There will be two independent datasets (one for patient survey, and one for HCP survey). All analyses will be descriptive.

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

Categorical variables (including Yes/No or True/False questions) will be described as the total number (of valid responses) and percentage per response category. In case of MCQs, the number and percentage of each option will be reported.

9.6.2. Planned Analyses

The main analyses will be for the overall datasets (all countries), for the EU countries (all countries excluding the UK), and for each individual country including analyses of the UK datasets only to respond to MHRA's concurrent request to assess the effectiveness of RMMs in that region.

The patient dataset will subsequently be analyzed by indication (migraine and epilepsy), and further sub-group analyses performed by age group.

The HCP dataset will subsequently be analyzed by 1) HCP category: GPs (including specialists in internal medicine), Other specialists managing epilepsy and/or migraine, OB/GYN (including midwives), Pharmacists, and by 2) medical specialty: GPs, specialists in internal medicine, neurologists (including neuro-pediatricians), psychiatrists, (general) pediatricians, OB/GYN (including midwives), and pharmacists.

Exploratory analyses will be performed for each sub-group by individual country, as supported by the data.

9.6.2.1. Questionnaire Analysis

For each question, the proportion of respondents answering correctly will be presented.

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, behavior) as follows:

- Awareness: individual score calculated as the proportion of correct responses to awareness questions (having received /having had access to and having read the DHPC and EMs). Success is defined as a score of at least 80%.
- Knowledge: individual score calculated as the proportion of correct responses among all the sub-questions related to knowledge. Successful knowledge of the newly implemented RMMs is defined as a score of at least 80%.
- Behavior: individual score calculated as the proportion of correct/desirable responses among all the sub-questions related to behavior. Successful behavior is defined as a score of at least 80%.

For each dimension, the number and proportion of participants who correctly responded to at least 80% of questions for awareness, knowledge or behavior, will be calculated. Success for each dimension is defined as having at least 80% of successful participants (i.e., with individual success scores of at least 80%). The denominator for awareness, knowledge and behavior dimensions will be the total number of participants who completed the full questionnaire. For the awareness domain, the proportion of HCPs who responded that they have not received / have not had access to any of the materials or who are unsure, and who prematurely ended the survey, will be calculated. The group who prematurely ended the survey and the group who completed the survey (i.e., reported being aware of receiving/having access to at least one of the materials) will be descriptively compared using demographic characteristics. This will generate insight into accessibility and effectiveness of the distribution of the EMs in the target HCP populations.

The same analysis will be performed for individual success threshold scores of 70%, 90%, and 100% of correct responses for each dimension.

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 or above the defined threshold of at least 80% of successful participants.

There will be only one final analysis after completion of all questionnaires and their recording in the database.

9.6.3. Missing Values

The aim is to have completeness of the data and no missing values. Missing data can undermine the ability of this study to make valid inference by introducing bias. The on-line survey will include programming logic to reduce missing data. If data are still missing, then an assessment of the amount of missingness and pattern of missingness will be performed. A non-response bias analysis, containing appropriate mechanisms and assumptions for the missing data, will be conducted. Finally, a summary of the missing values will be provided. Further details will be included in the SAP.

9.6.4. Interim Analysis

No interim analyses will be performed for this study.

9.7. Quality Control

9.7.1. Survey Content Validation

The questionnaires will be tested by a representative sample (based on the spectrum of HCP and patient characteristics) of 6 HCPs and 6 patients overall (one each, per country) to test comprehensibility, consistency, and appropriateness of the language used in the HCP and patient surveys. The questionnaires will be tested for their clarity before they are implemented. Checks for leading questions which may suggest a specific answer for any reason; for example, social desirability, will be implemented.

This testing will be conducted through a series of cognitive debriefing interviews.

9.7.2. Data Collection and Ongoing Data Quality Control

The questionnaires will be translated from English into the local language using back-and-forth translation to ensure an accurate translation of the local versions of the questionnaires. Translation and back translation will be performed by a certified translation vendor. Translation certificates will be provided for each translated language version of the questionnaires.

Multiple reminders as described in Section 9.2.1.3. will be sent to potential participants and partial completers, as well as incentives will be offered to maximize the response rate.

Collected data will be entered and stored in a database specific to the survey and the country. For each survey, a study database will be created by merging databases of each country. Personal identifying information (PII) will be stored separately from the survey data by recruitment vendors and Syneos Health. No PII will be collected via the on-line survey, except in Germany where personal information must be collected from participating physicians for the purpose of legally required notifications of Transfer of Value (ToV) to the relevant regulatory authorities within Germany. Each completed survey will be assigned a unique system generated Study ID/Response ID. Study ID/response IDs will be provided to recruitment vendors for association with each participant. Syneos Health study team will not hold the participant ID key for any patient or HCP participant recruited via recruitment vendors, for any HCP participant recruited via HCP lists, or for any patient (or parent/caregiver) referred via HCPs.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values
- Cross-check the consistency of data for related variables (if feasible)

All survey aspects from protocol development to the reporting of the results will be conducted according to the applicable Standard Operating Procedures (SOPs) of Syneos Health.

9.8. Limitations of the Research Methods

While there are many advantages of using on-line surveys as a method of data collection, there are also potential limitations. Some of these limitations are inherent in all survey research, while others are unique to distributing surveys via on-line platforms. These potential limitations, as well as any steps that will be taken to minimize each potential limitation, are described below.

9.8.1. Accuracy of Self-reported Data

One potential limitation is that participants may not provide accurate and honest responses to all survey questions – whether consciously or unconsciously. Response inaccuracies may occur for various reasons, including (a) unwillingness to answer truthfully, (b) inability to accurately remember or report about themselves, (c) confusion with directions or questions, and/or (d) the restrictiveness of rating scales.

To enhance the likelihood that participants will answer honestly and accurately, several steps will be taken:

- Survey instructions will include a statement about the importance of answering truthfully and honestly.
- Care will be taken to ensure directions and questions are clear and understandable.
- Knowledge and behavior questions will include an "I don't know" response option, where relevant.
- An "attention check" question will also be included, to verify that participants are reading the questions and answering honestly.

9.8.2. Selection Bias

Different potential sources of selection bias are associated with survey research and affect the generalizability of results. First, in web-based surveys, only participants who have an active email address and are willing (and able) to answer a questionnaire on-line will respond. These participants may not be fully representative of the whole targeted population.

Second, the primary source of recruitment of HCPs will be HCP consumer panel(s) and the primary source of patient recruitment will be a patient consumer panel. Participants in a panel may not be fully representative of the whole targeted population. We aim to mitigate this using a second source of recruitment of HCPs via HCP lists (after removing duplicates). These HCPs may better represent the population; however, they still need to be willing to take part in the research. For patients (and parents/caregivers) who are referred via HCPs (from HCP lists), selection bias will be minimized by instructing sequential recruitment. However, like for HCPs, patients (and parents/caregivers) need to accept their participation.

To quantify any selection bias, the distribution of patient and HCPs characteristics (e.g., country, specialty, and other relevant demographic information) will be compared between participants and non-participants and margin of error using 95% confidence level will be calculated.

9.8.3. Information Bias

Web-based surveys may promote information bias that may result from social desirability, which refers to the tendency of participants to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior, e.g., participants can copy-paste or refer to information gathered on-line instead of giving their own opinions.

Recall bias may lead to an underestimation of the HCPs and patients recalling having received EM. In an attempt to comment about these differences in accuracy or completeness of the recollections retrieved when answering the survey, if any, we will provide updated information about the distribution of EMs in each participating country.

To avoid potential bias due to a difference in duration between fielding the survey and rollout of EMs, fielding in each country will be no sooner than 12 months post-rollout of EMs.

9.8.4. Non-Response Bias

Another potential limitation is that participants may not answer all survey questions, which results in item non-response, as those who choose to respond to a question may be different from those who did not respond. To mitigate the likelihood of random item non-response, a common data validation feature will be used when programming each of the on-line surveys. Participants will be required to answer a question prior to moving to the next question. To mitigate the likelihood of item non-response due to incomplete surveys, only complete surveys will be included in the data analysis.

9.8.5. Other Design Limitations

Finally, important potential design limitations are the inability to achieve the target sample sizes overall and by country, and the lack of a clear criterion for success (aka. success threshold) at both the individual patient level and the study level (a measure of 80% is currently proposed for both).

To limit the impact on the interpretability and generalizability of the findings, stratification of both HCP and patient samples by sub-populations will be implemented. To further mitigate the risk of not achieving the overall target sample size and to more realistically reflect the participant recruitment potential, pragmatic sample size adjustments have been made including over-, and under sampling by indication, HCP categories/sub-specialties, and countries (see Section 9.4.1.1.

Subsequently, results will be weighed according to the most up-to-date number and distribution of patients being prescribed topiramate by indication and by country, and the most up-to-date number and distribution of HCPs by medical specialty and who are receiving EM in each country. This would correct any over- or under-sampling that may have occurred and would make the results more generalizable and representative to the entire population across the participating countries. The latter procedure will be described in detail in the SAP.

Whilst the success threshold of 80% for knowledge and behavior is deemed reasonable given the lack of a clear criterion for such a threshold (see Section 9.3.1.), results will need to be carefully interpreted with the 80% success threshold being used as a subjective guide to interpret the overall level of satisfaction of the effectiveness of the RMMs. To aid in this interpretation, further analyses will be performed to show for each dimension the number and proportion of participants with composite scores at different success thresholds of ≥70% and ≥90% (see Section 9.6.2.1.).

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to Janssen on behalf of the Topiramate Safety Consortium. Each survey will be provided to verified and pre-consented HCPs and pre-consented patients that are part of separate proprietary consumer panels. Data collected (see variables described in Section 9.3) will remain confidential. Only aggregated data will be analyzed and communicated in a report.

The study will be conducted in agreement with the Regulation (EU) 2016/679 of the European Parliament on the protection of natural persons regarding the processing of personal data and on the free movement of such data (General Data Protection Regulation).

10.1. Participant Information and Consent

Syneos Health and its recruitment vendors will ensure that the national and European data protection and ethical requirements are met for the patients and HCPs. Within the HCP Participation Agreement and Patient ICF, which will be shared electronically ahead of survey completion, survey participants will be informed about the purpose of the survey, the nature of the transmitted data, the intended use of these data, recipients of these data, storage of their data, their right of access to and rectification of their personal data, as well as their right of objection to use their data or to Syneos Health keeping their data. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations. Potential participants will be told that their participation is entirely voluntary and that they may withdraw their participation in the electronic survey at any time.

10.2. Regulatory Approval/Notification and Independent Ethics Committee (IEC) Submission

To ensure the quality and integrity of research, this study will be conducted under the guidelines for GVPs and good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws, and regulations.

The study protocol will be submitted to the responsible Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for its review/approval whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations.

A national coordinating investigator in each country, where required, will be responsible for providing the IRB/IEC with current and complete copies of all documents, as required by local regulations.

During study conduct, the national coordinating investigator, where required, will provide the IEC/IRB with:

- any summaries of the status of the study at intervals stipulated by the IEC/IRB (if applicable)

- any substantial amendments to the aforementioned documents for the IEC/IRB's review and approval before implementation of the change(s). Any protocol amendment(s) that are purely administrative are excluded, with no consequences for data collection.

At the end of the study, where required by local regulations, the national coordinating investigator, where required, will notify the IEC/IRB about the study completion.

11. COLLECTION AND REPORTING OF SAFETY DATA AND COMPLAINTS

This study is a survey with HCPs and patients to assess the effectiveness of the newly implemented RMMs. Hence, this survey does not involve data collection on clinical endpoints on individual patients, does not include questions that could potentially identify a safety event (defined as an Adverse Event (AE), Special Situation or Product Quality Complaint with or without AE), and does not provide an opportunity (e.g., free text field) where study participants could provide information that may constitute a safety event. Therefore, safety events will not be systematically solicited as part of this study.

Further, routine communication with study participants via email or phone with a study team member (i.e., Syneos Health staff or an associated team member from any recruitment vendor is not planned during the conduct of both surveys. However, it is possible that a study participant may provide information to a study team member that could constitute a safety event while in conversation about the survey for any reason. In case a safety event for any topiramate mono-component product is reported by a study participant to a study team member, the study team member is obliged to report the safety event directly to the market authorization holder (MAH) of the concerned brand (if brand is mentioned) or to all MAHs of the consortium in case the brand is unknown within one (1) business day or in any event no later than three (3) calendar days. During the study, the MAHs will report individual case safety reports (ICSRs) to health authorities according to all applicable local and global regulations and MAHs' processes.

All safety events collected during the study will be summarized in the final study report.

All relevant study team members involved in providing the services of the study (including, but not limited to, employees, consultants, contractors, and subcontractors) will undergo adequate pharmacovigilance training.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Topiramate Safety Consortium will register and/or disclose the existence of and the results of clinical studies as required by law. The study will be registered in the publicly available Heads of Medicines Agencies (HMA)-EMA Catalogues of RWD sources and studies (previously known as EU PAS register). Updates to the study protocol in case of substantial amendments and an abstract of the final study report will also be uploaded in the HMA-EMA Catalogues. The results of the study will be reported in a clinical study report.

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ANNEX 1: LIST OF STANDALONE DOCUMENTS

Title	Reference No	Date
Contact information for Janssen on behalf of the Topiramate Safety Consortium and all investigators	N/A	N/A
Informed Consent Form	N/A	N/A
HCP Survey	EDMS-RIM-1314476	12 June 2025
Patient Survey	EDMS-RIM-1314481	12 June 2025

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				
	1.1.1 Start of data collection[a]	X	☐	☐	6.
	1.1.2 End of data collection[b]	X	☐	☐	6.
	1.1.3 Progress report(s)	☐	☐	X	6.
	1.1.4 Interim report(s)	☐	☐	X	6.
	1.1.5 Registration in the EU PAS Register®	X	☐	☐	6.
	1.1.6 Final report of study results.	X	☐	☐	6.

Comments:

Study is registered in HMA-EMA Catalogues of RWD sources and studies (formerly the EU PAS Register)

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	X	☐	☐	8.
	2.1.1 Why conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	7.3.
	2.1.2 The objective(s) of the study?	X	☐	☐	8.2.
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	X	☐	☐	9.2.1.
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	X	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	X	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X	☐	☐	9.1.
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	9.1.
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X	☐	☐	9.3.
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	X	

[a] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[b] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	X	☐	☐	11.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	X	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	X	☐	☐	9.2.2.
	4.2.2 Age and sex	X	☐	☐	9.3.
	4.2.3 Country of origin	X	☐	☐	9.1.1
	4.2.4 Disease/indication	X	☐	☐	9.3.
	4.2.5 Duration of follow-up	X	☐	☐	9.2.2.
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	9.2.1.

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	X	☐	☐	9.3.
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	X	☐	☐	9.7.1.
5.3	Is exposure categorized according to time windows?	☐	X	☐	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	X	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	X	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	X	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	X	☐	☐	9.6.2.1.
6.2	Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	9.3.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	X	☐	☐	9.8.
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	X	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	X	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	X	☐	☐	9.8.2.
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X	☐	☐	9.8.3.

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	X	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	X	☐	☐	9.4.
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	9.4.
9.1.3 Covariates and other characteristics?	☐	☐	X	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	X	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	X	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	X	

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	X	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	X	☐	
	9.3.3 Covariates and other characteristics?	☐	☐	X	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	X	☐	☐	9.6.
10.2	Is study size and/or statistical precision estimated?	X	☐	☐	9.7.1. 9.4.1.
10.3	Are descriptive analyses included?	X	☐	☐	9.6.
10.4	Are stratified analyses included?	☐	☐	X	
10.5	Does the plan describe methods for analytic control of confounding?	☐	X	☐	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	X	☐	
10.7	Does the plan describe methods for handling missing data?	X	☐	☐	9.6.3. 9.8.4.
10.8	Are relevant sensitivity analyses described?	☐	☐	X	

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	10.1.
11.2	Are methods of quality assurance described?	X	☐	☐	9.7.
11.3	Is there a system in place for independent review of study results?	☐	☐	X	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	X	☐	☐	9.8.3.
12.1.2 Information bias?	X	☐	☐	9.8.3.
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	X	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X	☐	☐	9.4. 9.5.

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	X	☐	☐	10.2.
13.2 Has any outcome of an ethical review procedure been addressed?	X	☐	☐	10.2.
13.3 Have data protection requirements been described?	X	☐	☐	10.1.

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	X	☐	☐	5.

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X	☐	☐	12.
15.2 Are plans described for disseminating study results externally, including publication?	X	☐	☐	12.

Comments:

ANNEX 3. RISK MINIMIZATION MEASURES RELATED TO PREGNANCY – EXISTING AND NEWLY IMPLEMENTED

Existing risk minimization measures

- Summary of Product Characteristics
  - Section 4.3 *Contraindications*
  - Section 4.4 *Special warnings and precautions for use*
  - Section 4.5 *Interaction with other medicinal products and other forms of interaction*
  - Section 4.6 *Fertility, pregnancy, and lactation*
- Patient Leaflet
  - Section 2 *WHAT YOU NEED TO KNOW BEFORE YOU TAKE TOPIRAMATE TABLETS*
- Legal Status: medicinal product restricted to medical prescription only

Newly implemented risk minimization measures (incl. safety communication tool)

- Education Materials
  - Health care professional guide including risk awareness form
  - Patient guide
- Direct healthcare professional communication (DHPC) with communication plan
- Visible warning on outer packaging
- Patient Card
- Requested updates to Summary of Product Characteristics
  - Section 4.2 *Posology and method of administration*
  - Section 4.3 *Contraindications*
  - Section 4.4 *Special warnings and precautions for use*
  - Section 4.5 *Interaction with other medicinal products and other forms of interaction*
  - Section 4.6 *Fertility, pregnancy, and lactation*
  - Black triangle
- Requested updates to Patient Leaflet
  - Section 2 *What you need to know before you take Topiramate*
  - Section 3 *How to take Topiramate*
  - Section 6 *Contents of the pack and other information*
  - Black triangle

ANNEX 4. LIST AND CONTACT DETAILS OF QPPVs OF REPRESENTED MAHs

Marketing Authorization Holder	Contact Person
LABORATORIOS COMBIX, S.L.U.	Ana I. Solórzano EU QPPV PPD
STADA: AFFILIATES OF STADA ARZNEIMITTEL AG (ALIUD PHARMA GMBH; CENTRAFARM B.V.; CICLUM FARMA UNIPESSOAL LDA.; EG S.P.A.; EUROGENERICS N.V./S.A.; LABORATORIO STADA, S.L.; STADA ARZNEIMITTEL GMBH; STADAPHARM GMBH)	Andreas Iwanowitsch PPD Pharmacovigilance, EU QPPV PPD
FARMOZ - SOCIEDADE TÉCNICO MEDICINAL, S.A.; PENTAFARMA - SOCIEDADE TÉCNICO-MEDICINAL, S.A.; TECNIMEDE ESPAÑA INDUSTRIA FARMACÉUTICA, S.A.; TECNIGEN, S.R.L.	Augusto Filipe QPPV PPD
LABORATORIOS NORMON, S.A.	Carlos Govantes QPPV PPD
GLENMARK ARZNEIMITTEL GMBH; GLENMARK PHARMACEUTICALS EUROPE LIMITED; GLENMARK PHARMACEUTICALS S.R.O.	Guenter Gartenmaier PPD EUQPPV PPD PPD
PHARMAZAC SA	PPD
ADAMED LABORATORIOS, S.L.U.	Eva Sobreviela PPD EU-QPPV PPD
ARROW GENERIQUES	Dr. Ludka Fyles, QPPV PPD
PUREN PHARMA GMBH & CO. KG	
AUROBINDO PHARMA B.V.	
AUROBINDO PHARMA ITALIA	
AUROVITAS SPAIN, S.A.U.	
AUROBINDO PHARMA (MALTA) LTD	
GENERIS FARMACÊUTICA, S.A.	
AUROBINDO PHARMA - MILPHARM LTD.	

Marketing Authorization Holder	Contact Person
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ORION CORPORATION	PPD PPD
JANSSEN-CILAG PHARMA GMBH, JANSSEN-CILAG NV, JOHNSON & JOHNSON S.E. D.O.O., JANSSEN-CILAG INTERNATIONAL NV, JANSSEN-CILAG S.R.O, JANSSEN-CILAG A/S, UAB "JOHNSON & JOHNSON", JANSSEN-CILAG OY, JANSSEN-CILAG, JANSSEN-CILAG GMBH, JANSSEN-CILAG PHARMACEUTICAL S.A.C.I., JANSSEN-CILAG KFT., JANSSEN-CILAG AB, JANSSEN SCIENCES IRELAND UC, JANSSEN-CILAG SPA, JANSSEN-CILAG BV, JANSSEN-CILAG FARMACÊUTICA, LDA., JOHNSON & JOHNSON D.O.O., JOHNSON & JOHNSON, S.R.O, JANSSEN-PHARMA, S.L., JANSSEN-CILAG LIMITED	Dr. Laurence Oster-Gozet, PharmD, PhD EU QPPV Pharma PPD Malgorzata Knurowska, MD UK QPPV Pharma PPD
MORNINGSIDE HEALTHCARE LTD	Dr. Vineet Kacker UK QPPV PPD
HORMOSAN PHARMA GMBH	Katja Funke PPD
DOC GENERICI S.R.L.	Marcella Falcone QPPV PPD
SANDOZ GMBH; SANDOZ PHARMACEUTICALS D.D.; 1A PHARMA GMBH; HEXAL AG; SANDOZ B.V.; SANDOZ S.P.A.; SANDOZ A/S	Mohamed Ali Kotal EU-QPPV & Head QPPV Office PPD

Marketing Authorization Holder	Contact Person
ROSEMONT PHARMACEUTICALS LIMITED	Hannah Abdulai PPD UK QPPV PPD
TOWA PHARMACEUTICAL S.A.	Patricia Haro EU QPPV PPD PPD
TEVA B.V; TEVA PHARMA – PRODUTOS FARMACÊUTICOS LDA; RATIOPHARM-COMERCIO E INDUSTRIA DE PRODUTOS FARMACEUTICOS LDA; RATIOPHARM GMBH; TEVA PHARMA S.L.U., TEVA SWEDEN AB; ACTAVIS GROUP PTC EHF.; TEVA PHARMA EAD	Iva Novak QPPV PPD
HEUMANN PHARMA GMBH & CO GENERICA KG, TORRENT PHARMA (UK) LIMITED AND TORRENT PHARMA (MALTA) LIMITED	Frank Laschewski QPPV PPD
KERN PHARMA, S.L.	Helena Gimeno EU-QPPV PPD
LABORATORIOS CINFA S.A.	Javier Barrado Catalán European QPPV PPD
NEURAXPHARM SPAIN, S.L.U. AND NEURAXPHARM ARZNEIMITTEL GMBH	Lucia Castrillo PPD / EU-QPPV PPD
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ZYDUS PHARMACEUTICALS UK LTD	Deval Kotadia PPD UK-QPPV/NCP PPD

Marketing Authorization Holder	Contact Person
CRESCENT PHARMA LTD	Amy Tanti PPD (QPPV) PPD
G.L. PHARMA GMBH	Doris Nussgruber QPPV, PPD

ANNEX 5. LIST OF AUTHORIZED TOPIRAMATE MONO-COMPONENT PRODUCTS

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
France	Accord Healthcare France Sas	Topiramate Accord	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
France	Accord Healthcare France Sas	Topiramate Accord	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
France	Accord Healthcare France Sas	Topiramate Accord	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
France	Accord Healthcare France Sas	Topiramate Accord	Topiramate 50mg	Film-Coated Tablet	Oral Use
France	Arrow Generiques	Topiramate Arrow Lab	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
France	Arrow Generiques	Topiramate Arrow Lab	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
France	Arrow Generiques	Topiramate Arrow Lab	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
France	Biogaran	Topiramate Bgr	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
France	Biogaran	Topiramate Bgr	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
France	Biogaran	Topiramate Bgr	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
France	Janssen-Cilag	Epitomax	Topiramate 15mg Capsule	Capsule, Hard	Oral Use
France	Janssen-Cilag	Epitomax	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
France	Janssen-Cilag	Epitomax	Topiramate 50mg Capsule	Capsule, Hard	Oral Use
France	Janssen-Cilag	Epitomax	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
France	Janssen-Cilag	Epitomax	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
France	Janssen-Cilag	Epitomax	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
France	Sandoz	Topiramate Sandoz	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
France	Sandoz	Topiramate Sandoz	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
France	Viatris Sante (Lyon)	Topiramate Tablets 50 mg	Topiramate Viatris 50 mg, comprimé pelliculé	Film-Coated Tablet	Oral Use
France	Viatris Sante (Lyon)	Topiramate Tablets 100 mg	Topiramate Viatris 100 mg,	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
			comprimé pelliculé		
France	Viatris Sante (Lyon)	Topiramate Tablets 200 mg	Topiramate Viatris 200 mg, comprimé pelliculé	Film-Coated Tablet	Oral Use
Germany	1 A Pharma Gmbh	Topiramat 1 A Pharma	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	1 A Pharma Gmbh	Topiramat 1 A Pharma	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	1 A Pharma Gmbh	Topiramat 1 A Pharma	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	1 A Pharma Gmbh	Topiramat 1 A Pharma	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Topiramat Al	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Topiramat Al	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Topiramat Al	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Topiramat Al	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Topiramat Migräne Al	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Aliud Pharma Gmbh	Topiramat Migräne Al	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Glenmark Arzneimittel Gmbh	Topiramat Glenmark	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Glenmark Arzneimittel Gmbh	Topiramat Glenmark	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Glenmark Arzneimittel Gmbh	Topiramat Glenmark	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Glenmark Arzneimittel Gmbh	Topiramat Glenmark	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Heumann Pharma Gmbh & Co. Generica Kg	Topiramat Heumann	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Heumann Pharma Gmbh & Co. Generica Kg	Topiramat Heumann	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Heumann Pharma Gmbh & Co. Generica Kg	Topiramat Heumann	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Heumann Pharma Gmbh & Co. Generica Kg	Topiramat Heumann	Topiramate 400mg Tablet	Film-Coated Tablet	Oral Use
Germany	Heumann Pharma Gmbh & Co. Generica Kg	Topiramat Heumann	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Germany	Hormosan Pharma Gmbh	Topiramat Hormosan	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Hormosan Pharma Gmbh	Topiramat Hormosan	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Hormosan Pharma Gmbh	Topiramat Hormosan	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Hormosan Pharma Gmbh	Topiramat Hormosan	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Janssen-Cilag Gmbh	Topamax	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
Germany	Janssen-Cilag Gmbh	Topamax	Topiramate 50mg Capsule	Capsule, Hard	Oral Use
Germany	Janssen-Cilag Gmbh	Topamax	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Janssen-Cilag Gmbh	Topamax	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Janssen-Cilag Gmbh	Topamax	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Janssen-Cilag Gmbh	Topamax	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Topiramat Neuraxpharm	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Topiramat Neuraxpharm	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Topiramat Neuraxpharm	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Neuraxpharm Arzneimittel Gmbh	Topiramat Neuraxpharm	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Aurobindo	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Aurobindo	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Aurobindo	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Aurobindo	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Puren	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Puren	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Puren	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Puren Pharma Gmbh & Co. Kg	Topiramat Puren	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Migräne Stada	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Migräne Stada	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Migräne Stada	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Stada	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Stada	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Stada	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Germany	Stadapharm Gmbh	Topiramat Stada	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Poland	Accord Healthcare Polska Sp. z o.o.	Topiramat Accord	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Poland	Accord Healthcare Polska Sp. z o.o.	Topiramat Accord	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Poland	Accord Healthcare Polska Sp. z o.o.	Topiramat Accord	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Poland	Accord Healthcare Polska Sp. z o.o.	Topiramat Accord	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Poland	Bausch Health Ireland Limited	Etopro	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Poland	Bausch Health Ireland Limited	Etopro	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Poland	Bausch Health Ireland Limited	Etopro	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Poland	Bausch Health Ireland Limited	Etopro	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Poland	Janssen-Cilag International Nv	Topamax,	Topiramate 15mg Capsule	Capsule, Hard	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Poland	Janssen-Cilag International Nv	Topamax,	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
Poland	Janssen-Cilag International Nv	Topamax,	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Poland	Janssen-Cilag International Nv	Topamax,	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Poland	Janssen-Cilag International Nv	Topamax,	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Poland	Janssen-Cilag International Nv	Topamax,	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Arzneimittel Gmbh	Toramat	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Arzneimittel Gmbh	Toramat	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Arzneimittel Gmbh	Toramat	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Arzneimittel Gmbh	Toramat	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Bohemia S.R.O.	Topiramate Farmax	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Bohemia S.R.O.	Topiramate Neuraxpharm	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Poland	Neuraxpharm Bohemia S.R.O.	Topiramate Neuraxpharm	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Poland	Orion Corporation	Oritop	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Poland	Orion Corporation	Oritop	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Accord Healthcare S.L.U.	Roklisan	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Accord Healthcare S.L.U.	Roklisan	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Accord Healthcare S.L.U.	Roklisan	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Accord Healthcare S.L.U.	Roklisan	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Adamed Laboratorios, S.L.U.	Acomicil	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Adamed Laboratorios, S.L.U.	Acomicil	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Spain	Adamed Laboratorios, S.L.U.	Acomicil	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Adamed Laboratorios, S.L.U.	Acomicil	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Arafarma Group, S.A	Fagodol	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Arafarma Group, S.A	Fagodol	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Arafarma Group, S.A	Fagodol	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Arafarma Group, S.A	Fagodol	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Aurovitas Spain,s.A.U.	Topiramato Aurovitas	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Aurovitas Spain,s.A.U.	Topiramato Aurovitas	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Aurovitas Spain,s.A.U.	Topiramato Aurovitas	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Aurovitas Spain,s.A.U.	Topiramato Aurovitas	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Farmalider, S.A.	Topiramato Farmalider	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Farmalider, S.A.	Topiramato Farmalider	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Farmalider, S.A.	Topiramato Farmalider	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Farmalider, S.A.	Topiramato Farmalider	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax Dispersable	Topiramate 15mg Capsule	Capsule, Hard	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax Dispersable	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax Dispersable	Topiramate 50mg Capsule	Capsule, Hard	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Janssen-Pharma, S.L.	Topamax	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Kern Pharma, S.L.	Topiramato Kern Pharma	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Kern Pharma, S.L.	Topiramato Kern Pharma	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Kern Pharma, S.L.	Topiramato Kern Pharma	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Kern Pharma, S.L.	Topiramato Kern Pharma	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorio Stada, S.L.	Topiramato Stada	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Spain	Laboratorio Stada, S.L.	Topiramato Stada	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorio Stada, S.L.	Topiramato Stada	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorio Stada, S.L.	Topiramato Stada	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Aurobindo S.L.U.	Topiramato Aurobindo	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Aurobindo S.L.U.	Topiramato Aurobindo	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Aurobindo S.L.U.	Topiramato Aurobindo	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Cinfa, S.A.	Topiramato Cinfa	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Cinfa, S.A.	Topiramato Cinfa	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Cinfa, S.A.	Topiramato Cinfa	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Cinfa, S.A.	Topiramato Cinfa	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Combix, S.L.U.	Topiramato Pharma Combix	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Combix, S.L.U.	Topiramato Pharma Combix	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Combix, S.L.U.	Topiramato Pharma Combix	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Normon, S.A.	Topiramato Normon	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Normon, S.A.	Topiramato Normon	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Normon, S.A.	Topiramato Normon	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Laboratorios Normon, S.A.	Topiramato Normon	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Neuraxpharm Spain, S.L.U.	Topiramato Qualigen	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Neuraxpharm Spain, S.L.U.	Topiramato Qualigen	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Neuraxpharm Spain, S.L.U.	Topiramato Qualigen	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Neuraxpharm Spain, S.L.U.	Topiramato Qualigen	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Spain	Ratiopharm España S.A.	Topiramato Ratiopharm	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Ratiopharm España S.A.	Topiramato Ratiopharm	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Ratiopharm España S.A.	Topiramato Ratiopharm	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Ratiopharm España S.A.	Topiramato Ratiopharm	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Sandoz Farmacéutica, S.A.	Topiramato Sandoz	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Sandoz Farmacéutica, S.A.	Topiramato Sandoz	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Sandoz Farmacéutica, S.A.	Topiramato Sandoz	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Sandoz Farmacéutica, S.A.	Topiramato Sandoz	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tarbis Farma, S.L.	Topiramato Tarbis	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tarbis Farma, S.L.	Topiramato Tarbis	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tarbis Farma, S.L.	Topiramato Tarbis	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tarbis Farma, S.L.	Topiramato Tarbis	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tecnimede España Ind. Fca., S.A.	Topiramato Tecnigen	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tecnimede España Ind. Fca., S.A.	Topiramato Tecnigen	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tecnimede España Ind. Fca., S.A.	Topiramato Tecnigen	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Tecnimede España Ind. Fca., S.A.	Topiramato Tecnigen	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Teva Pharma S.L.U.	Topiramato Teva	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Teva Pharma S.L.U.	Topiramato Teva	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Teva Pharma S.L.U.	Topiramato Teva	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Teva Pharma S.L.U.	Topiramato Teva	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Spain	Towa Pharmaceutical S.A	Topiramato Pensa Pharma	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Spain	Towa Pharmaceutical S.A	Topiramato Pensa Pharma	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Spain	Towa Pharmaceutical S.A	Topiramato Pensa Pharma	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Spain	Towa Pharmaceutical S.A	Topiramato Pensa Pharma	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Spain	Viatris Pharmaceuticals SL	Topiramate Tablets 25 mg	Topiramato Viatris 25 mg comprimidos recubiertos con pelicula EFG	Film-Coated Tablet	Oral Use
Spain	Viatris Pharmaceuticals SL	Topiramate Tablets 50 mg	Topiramato Viatris 50 mg comprimidos recubiertos con pelicula EFG	Film-Coated Tablet	Oral Use
Spain	Viatris Pharmaceuticals SL	Topiramate Tablets 100 mg	Topiramato Viatris 100 mg comprimidos recubiertos con pelicula EFG	Film-Coated Tablet	Oral Use
Spain	Viatris Pharmaceuticals SL	Topiramate Tablets 200 mg	Topiramato Viatris 200 mg comprimidos recubiertos con pelicula EFG	Film-Coated Tablet	Oral Use
Sweden	1A Farma	Topiramat 1A Farma	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Sweden	1A Farma	Topiramat 1A Farma	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Sweden	1A Farma	Topiramat 1A Farma	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Sweden	1A Farma	Topiramat 1A Farma	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Accord Healthcare B.V.	Topiramat Accord	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Accord Healthcare B.V.	Topiramat Accord	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Accord Healthcare B.V.	Topiramat Accord	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Accord Healthcare B.V.	Topiramat Accord	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Actavis Group Ptc Ehf.	Topiramat Actavis	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Actavis Group Ptc Ehf.	Topiramat Actavis	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Actavis Group Ptc Ehf.	Topiramat Actavis	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Actavis Group Ptc Ehf.	Topiramat Actavis	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 15mg Capsule	Capsule, Hard	Oral Use
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 50mg Capsule	Capsule, Hard	Oral Use
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Janssen-Cilag Ab	Topimax	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Orion Corporation	Topiramat Orion	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Orion Corporation	Topiramat Orion	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Orion Corporation	Topiramat Orion	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Orion Corporation	Topiramat Orion	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Ratiopharm Gmbh	Topiramat Ratiopharm	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
Sweden	Ratiopharm Gmbh	Topiramate Ratiopharm	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord Healthcare	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord Healthcare	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord Healthcare	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord Healthcare Limited	Topiramate Accord Healthcare	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Accord-Uk Limited	Topiramate Accord-Uk	Topiramate 50mg Capsule	Capsule, Hard	Oral Use
United Kingdom (Northern Ireland)	Actavis Uk Ltd.	Topiramate Accord	Topiramate 15mg Capsule	Capsule, Hard	Oral Use
United Kingdom (Northern Ireland)	Actavis Uk Ltd.	Topiramate Accord	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
United Kingdom (Northern Ireland)	Crescent Pharma Limited	Topiramate Crescent	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Crescent Pharma Limited	Topiramate Crescent	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Crescent Pharma Limited	Topiramate Crescent	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Crescent Pharma Limited	Topiramate Crescent	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Generics (UK) Ltd T/A Mylan : UK	Topiramate Tablets 25 mg	Topiramate Mylan 25 mg Film-coated Tablets	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Generics (UK) Ltd T/A Mylan : UK	Topiramate Tablets 50 mg	Topiramate Mylan 50 mg Film-coated Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
United Kingdom (Northern Ireland)	Generics (UK) Ltd T/A Mylan : UK	Topiramate Tablets 100 mg	Topiramate Mylan 100 mg Film-coated Tablets	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Generics (UK) Ltd T/A Mylan : UK	Topiramate Tablets 200 mg	Topiramate Mylan 200 mg Film-coated Tablets	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Glenmark Pharmaceuticals Europe Limited	Topiramate Glenmark	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Glenmark Pharmaceuticals Europe Limited	Topiramate Glenmark	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Glenmark Pharmaceuticals Europe Limited	Topiramate Glenmark	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Glenmark Pharmaceuticals Europe Limited	Topiramate Glenmark	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax Sprinkle	Topiramate 15mg Capsule	Capsule, Hard	Oral Use
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax Sprinkle	Topiramate 25mg Capsule	Capsule, Hard	Oral Use
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax Sprinkle	Topiramate 50mg Capsule	Capsule, Hard	Oral Use
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Janssen-Cilag Limited	Topamax	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Milpharm Limited	Topiramate Milpharm	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Milpharm Limited	Topiramate Milpharm	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Milpharm Limited	Topiramate Milpharm	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Milpharm Limited	Topiramate Milpharm	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Morningside Healthcare Ltd	Topiramate Morningside	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Morningside Healthcare Ltd	Topiramate Morningside	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Morningside Healthcare Ltd	Topiramate Morningside	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Morningside Healthcare Ltd	Topiramate Morningside	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Rosemont Pharmaceuticals Limited	Topiramate	Topiramate 10mg/Ml	Oral Suspension	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
United Kingdom (Northern Ireland)	Rosemont Pharmaceuticals Limited	Topiramate	Topiramate 20mg/Ml	Oral Suspension	Oral Use
United Kingdom (Northern Ireland)	Teva Uk Limited	Topiramate Teva	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Teva Uk Limited	Topiramate Teva	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Teva Uk Limited	Topiramate Teva	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Teva Uk Limited	Topiramate Teva	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Torrent Pharma (Uk) Ltd.	Topiramate Torrent	Topiramate 100mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Torrent Pharma (Uk) Ltd.	Topiramate Torrent	Topiramate 200mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Torrent Pharma (Uk) Ltd.	Topiramate Torrent	Topiramate 25mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Torrent Pharma (Uk) Ltd.	Topiramate Torrent	Topiramate 50mg Tablet	Film-Coated Tablet	Oral Use
United Kingdom (Northern Ireland)	Zydus Pharmaceuticals UK Ltd	Topiramate Zydus Pharmaceuticals UK	Topiramate 20 mg/ml Oral solution	Oral Solution	Oral Use
United Kingdom (Northern Ireland)	Cadila Pharmaceuticals Limited	Topiramate Cadila	Topiramate 25 mg Tablets	Film coated tablets	Oral Use
United Kingdom	Cadila Pharmaceuticals Limited	Topiramate Cadila	Topiramate 50 mg Tablets	Film coated tablets	Oral Use

Authorization Country	Marketing Authorization Holder	Short Product Name	INN/Active Substance + Strength	Pharmaceutical Form	Route of Administration
(Northern Ireland)					
United Kingdom (Northern Ireland)	Cadila Pharmaceuticals Limited	Topiramate Cadila	Topiramate 100 mg Tablets	Film coated tablets	Oral Use
United Kingdom (Northern Ireland)	Cadila Pharmaceuticals Limited	Topiramate Cadila	Topiramate 200 mg Tablets	Film coated tablets	Oral Use

Source: EMA's Annex I List of Medicinal Products and Presentation (https://www.ema.europa.eu/en/documents/referral/topiramate-article-31-referral-annex-i_en.pdf). This list has been modified to include topiramate mono-component products in the study countries. As part of the protocol version dated 19 March 2026, products have been added or removed, and certain MAH names and product details have been updated based on information provided by respective MAHs.