Summary of Risk Management Plan for TOPIMAX® (Topiramate)

This is a summary of the risk management plan (RMP) for TOPIMAX (also known as TOPAMAX®, TOPAMAC®, and EPITOMAX™). The RMP details important risks of TOPIMAX, [how these risks can be minimized], and how more information will be obtained about TOPIMAX's risks and uncertainties (missing information).

TOPIMAX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals (HCPs) and patients on how TOPIMAX should be used.

Important new concerns or changes to the current ones will be included in updates of TOPIMAX's RMP.

I. The Medicine and What it is Used For

TOPIMAX is authorized for migraine prophylaxis and as monotherapy or adjunctive therapy for epilepsy (see SmPC for the full indication). It contains topiramate as the active substance and it is given as an oral tablet (hard capsules of 15 mg, 25 mg and 50 mg and film-coated tablets of 25 mg, 50 mg, 100 mg and 200 mg).

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of TOPIMAX, together with measures to minimize such risks and the proposed studies for learning more about TOPIMAX's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;

Important advice on the medicine’s packaging;

The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine’s legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of TOPIMAX, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of TOPIMAX are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TOPIMAX. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Acute myopia and secondary angle-closure glaucoma • Metabolic acidosis • Suicide/suicide ideation • Major congenital malformations with use during pregnancy • Fetal growth restriction
Important potential risks	• Neurodevelopmental disorders in children exposed to topiramate in utero
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Acute Myopia and Secondary Angle-closure Glaucoma	
Evidence for linking the risk to the medicine	Cases of acute myopia and secondary angle-closure glaucoma have been reported in association with TOPIMAX in clinical trials and in the postmarketing setting, and are also described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	According to a review, at least one-third of acute angle-closure glaucoma cases are related to an over-the-counter or prescription drug (Lachkar 2007). Risk factors for glaucoma in general include elevated internal eye pressure; increasing age; ethnic background (African Americans older than age 40 years); family history of glaucoma; comorbid medical conditions such as diabetes, heart disease, hypertension, and hypothyroidism; other eye conditions; and long-term corticosteroid use. (Mayo Clinic 2012). Being of Asian descent increases risk for acute angle-closure glaucoma (Mayo Clinic 2012). Acute angle-closure glaucoma can be induced by various local and systemic drugs, including adrenergic, anticholinergic, cholinergic, antidepressant, antianxiety, sulfa-based, and anticoagulant agents. (Lachkar 2007).

Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.4 and 4.8. • PL Sections 2 and 4. • Legal status: medicinal product restricted to medical prescription only. **Additional risk minimization measures:** None
Important Identified Risk: Metabolic Acidosis	
Evidence for linking the risk to the medicine	Cases of metabolic acidosis have been reported in association with TOPIMAX in clinical trials and in the postmarketing setting, and are also described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	Metabolic acidosis could be caused due to increased acid load, excessive loss of gastrointestinal bicarbonate, impaired excretion of dietary acid load, and excessive loss of renal bicarbonate (Patient.co.uk 2013).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.4, 4.8, and 4.9. • PL Sections 2 and 4. • Legal status: medicinal product restricted to medical prescription only. **Additional risk minimization measures:** None
Important Identified Risk: Suicide/Suicide Ideation	
Evidence for linking the risk to the medicine	Cases of suicide and suicide ideation have been reported in association with TOPIMAX in clinical trials and in the postmarketing setting, and are also described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	Risk factors for a repeated suicide attempt could include a previous attempt, being a victim of sexual abuse, poor global functioning, having a psychiatric disorder, being on psychiatric treatment, depression, anxiety, and alcohol abuse or dependence. Caucasian ethnicity, having a criminal record, having any mood disorders, bad family environment, and impulsivity may also be correlated with suicide attempts. Risk factors for completed suicide are older age, suicide ideation, and history of suicide attempt (Beghi 2013). In all countries of the European region, men were almost 5 times more likely to commit suicides than women (average of 23.8 per 100,000 for men compared with 5.2 per 100,000 for women). Highest rates were also observed among people aged 65 years or older and among 45- to 59-year-olds (WHO 2014).

Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.4 and 4.8. • PL Sections 2 and 4. • Legal status: medicinal product restricted to medical prescription only. **Additional risk minimization measures:** None
Important Identified Risk: Major Congenital Malformations with Use During Pregnancy	
Evidence for linking the risk to the medicine	Cases of major congenital malformations in association with TOPIMAX during pregnancy have been reported in the postmarketing setting, and are also described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	A study based on data from the International Registry of Antiepileptic Drugs and Pregnancy (where 86% of the sample was from Europe) showed that risk of major congenital malformations was impacted not only by type of antiepileptic drug, but also by dose, and other variables such as parental history of major congenital malformations (Tomson 2011). Compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptic drugs in combination therapy. Effects were reported to be dose dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.6, and 4.8. • PL Section 2. • Visible warning on outer packaging. • Legal status: medicinal product restricted to medical prescription only. **Additional risk minimization measures:** • Educational materials - Healthcare Professional Guide Including a Risk Awareness Form - Patient Guide • Patient Card • Direct Healthcare Professional Communication (DHPC) with Communication Plan
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • PCSESPA0008: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey • PCSESPA0009: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study

Important Identified Risk: Fetal Growth Restriction	
Evidence for linking the risk to the medicine	Cases of fetal growth restriction have been reported in association with TOPIMAX in the postmarketing setting, and are also described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	Potential risk factors for fetal growth restriction include genetic factors and environmental factors such as socioeconomic status, maternal stress, maternal age, ethnicity, marital status of mother, medical risks before pregnancy (eg, chronic hypertension, renal diseases, etc), shorter birth intervals, multiple pregnancies, maternal lifestyles (poor nutrition, smoking, alcohol use), and poor prenatal care (Valero De Bernabé 2004). Maternal seizures and antiepileptic drug polytherapy have also been associated with poor fetal growth (Hernández-Díaz 2017).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.5 and 4.6. • PL Section 2. • Visible warning on outer packaging. • Legal status: medicinal product restricted to medical prescription only. **Additional risk minimization measures:** • Educational materials - HCP Guide Including a Risk Awareness Form - Patient Guide • Patient Card • DHPC with Communication Plan
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • PCSESPA0008: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey • PCSESPA0009: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study
Important Potential Risk: Neurodevelopmental Disorders in Children Exposed to Topiramate In Utero	
Evidence for linking the risk to the medicine	Cases and population-based studies of neurodevelopmental disorders (NDD) in association with TOPIMAX use during pregnancy have been reported in the postmarketing setting, and are also described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	In the 3 relevant literature reports assessing the potential association between topiramate exposure and NDD, covariates included the child's sex, and maternal characteristics such as age, psychiatric comorbidities, healthcare utilization, concurrent antidepressant and opioid use, smoking, and alcohol consumption (Bjørk 2022, Dreier 2023, Hernández-Díaz 2024). Neurodevelopmental disorders are more common in boys than in girls (May 2019), and older maternal age is reported to increase the risk for ASD (Kim 2022). Exposure

	to concomitant medications, alcohol, toxic substances, smoking, and psychostimulants during pregnancy have also been related to the development of NDD (Doi 2022).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.5 and 4.6. • PL Section 2. • Visible warning on outer packaging. • Legal status: medicinal product restricted to medical prescription only. **Additional risk minimization measures:** • Educational materials - HCP Guide Including a Risk Awareness Form - Patient Guide • Patient Card • DHPC with Communication Plan
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • PCSESPA0008: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey • PCSESPA0009: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

PCSESPA0008: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey

Research Question: What is the impact of the newly implemented risk minimization measures on the knowledge and self-reported behavior of HCPs who prescribe topiramate monocomponent products and of patients treated with topiramate monocomponent products in the United Kingdom and European Union?

Objectives

To assess the awareness of:

- Women of childbearing potential, treated with topiramate monocomponent products with respect to the receipt of the educational materials.
- HCPs with respect to the receipt of DHPC and HCP Guide for topiramate monocomponent products.

To assess the knowledge of:

- Women of childbearing potential treated with topiramate monocomponent 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 women of childbearing potential exposed to topiramate monocomponent products.

To assess the self-reported behavior of:

- Women of childbearing potential, treated with topiramate monocomponent products, with respect to measures to prevent exposed pregnancies.
- HCPs with respect to measures to prevent pregnancies among women of childbearing potential exposed to topiramate monocomponent products.

PCSESPA0009: Post-authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study

Purpose of the study: The overarching goal of the study is to describe the use of topiramate among women of childbearing potential with epilepsy or migraine during pre- and post-implementation periods of the newly implemented risk minimization measures and determine the effectiveness of the newly implemented risk minimization measures to reduce exposure to topiramate during pregnancy and for at least 4 weeks after discontinuing treatment with topiramate.

Primary Objectives

1. Compare the prevalence and incidence rate of topiramate use during the pre- and post-implementation periods of the newly implemented risk minimization measures among women of childbearing potential with epilepsy or migraine.
2. Describe pregnancy exposure to topiramate during the pre- and post-implementation periods of the newly implemented risk minimization measures among incident users of topiramate in women of childbearing potential with epilepsy or migraine.

Secondary Objectives

1. Compare the prevalence and incidence rate of topiramate use during the pre- and post-implementation periods of the newly implemented risk minimization measures among women of childbearing potential.
2. Describe pregnancy exposure to topiramate during the pre- and post-implementation periods of the newly implemented risk minimization measures among incident users of topiramate in women of childbearing potential.
3. Characterize the incident (new) users of topiramate during the pre- and post-implementation periods of the newly implemented risk minimization measures, separately, among overall women of childbearing potential (any indication) and among women of childbearing potential with epilepsy or migraine.

Exploratory Objectives

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

- Compare the incidence of topiramate use as first-line treatment during the pre- and post-implementation periods of the new risk minimization measures among women of childbearing potential with epilepsy or migraine.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for TOPIMAX.