PART VI: 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®, 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 (PL) give essential information to healthcare professionals 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 PL and SmPC addressed to patients and healthcare professionals;
- 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 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.

If important information that may affect the safe use of TOPIMAX is not yet available, it is listed under ‘missing information’ below.

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	• Nephrolithiasis • Acute myopia and secondary angle-closure glaucoma • Metabolic acidosis • Mood changes and depression • Suicide/suicide ideation • Major congenital malformations with use in pregnancy • Hypothermia with concomitant valproic acid • Oligohydrosis • Hyperammonemia with or without encephalopathy with or without concomitant valproic acid • Visual field defect • Decreased clearance in renal impairment • Decreased clearance in hepatic impairment
Important potential risks	• Low birth weight • Premature delivery
Missing information	• Use of TOPIMAX in neonatal seizures • Exposure of infants to TOPIMAX via breastfeeding • With long-term treatment of pediatric patients, the association between metabolic acidosis and nephrolithiasis, bone mineral density abnormalities, and delayed growth

II.B. Summary of Important Risks

Important Identified Risk: Nephrolithiasis	
Evidence for linking the risk to the medicine	Cases of nephrolithiasis 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.

Important Identified Risk: Nephrolithiasis	
	TOPIMAX is a carbonic anhydrase inhibitor, a class of compounds known to promote stone formation.
Risk factors and risk groups	Changes in dietary practices such as increased consumption of starchy foods, sodium, animal protein, and high fructose, as well as global warming, have been proposed as potential risk factors (Romero 2010). In a US National Health and Nutrition Examination Survey, kidney stones were more common among obese (11.2%) than normal weight individuals (6.1%), and obesity and diabetes were strongly associated with a history of kidney stones (Scales 2012). Other risk factors include family or personal history, being aged 40 years or older, male sex, dehydration, digestive diseases and surgery, and medical conditions such as renal tubular acidosis, cystinuria, hyperparathyroidism, and certain urinary tract infections (Mayo Clinic 2012d). Additional risk factors include hypercalciuria, and the administration of other medication associated with nephrolithiasis.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.5 and 4.8. • PL Sections 2, 3 and 4. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

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 2012c). Being of Asian descent increases risk for acute angle-closure glaucoma (Mayo Clinic 2012c). 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: Mood Changes and Depression	
Evidence for linking the risk to the medicine	Cases of mood changes and depression 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 depression could include family history of mental illness, chronic physical or mental disorders, having traumatic experiences as a child, major life changes, stress, limited social support, female gender, age (especially being elderly), certain medications, insomnia, and alcohol abuse (Mayo Clinic 2012b).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.8 and 4.9. • PL Section 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 In 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 4.3, 4.4, 4.6 and 4.8. • PL Section 2. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Important Identified Risk: Hypothermia with Concomitant Valproic Acid	
Evidence for linking the risk to the medicine	Cases of hypothermia with concomitant valproic acid use 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	Factors that could increase risk of developing hypothermia are older age (≥65 years), very young age (neonates and children), mental disorders (such as dementia), alcohol and drug use, certain medical conditions, and medications (Mayo Clinic 2011b).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.5. • PL Section 4. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Important Identified Risk: Oligohydrosis	
Evidence for linking the risk to the medicine	Cases of oligohydrosis 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	Most of the postmarketing reports of oligohydrosis have occurred in children. A review of cases suggested that the onset of the events

	occurred during warmer months of the year, based on the country of origin of the case, with 127 of the 194 cases having onset or being reported during May to September (PSUR 2007).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8. • PL Section 4. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Important Identified Risk: Hyperammonemia with or without Encephalopathy with or without Concomitant Valproic Acid	
Evidence for linking the risk to the medicine	Cases of hyperammonemia with or without encephalopathy with or without concomitant valproic acid 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	Among 121 noncirrhotic adult patients with seizures admitted to the emergency department of a Taiwan hospital, significant factors associated with hyperammonemia were generalized tonic-clonic seizures, male gender, bicarbonate, diabetes, and alcohol-related seizures (Hung 2011). A review of valproic acid-induced hyperammonemia case reports indicated risk factors to include higher doses of medication, concomitant use of other antiepileptic medications, and presence of congenital abnormalities of urea cycle (Mittal 2009).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.5 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: Visual Field Defect	
Evidence for linking the risk to the medicine	Cases of visual field defect 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	In a Chinese population-based study, visual field loss increased with age, intraocular pressure, and fasting blood glucose level (Wang YX 2012). Major causes were cataract, glaucoma, and diabetic retinopathy (Wang YX 2012). Antiepileptic treatment can also contribute to visual field defects based on a plethora of research on visual field defects in epileptic patients.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.7 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: Decreased Clearance in Renal Impairment	
Evidence for linking the risk to the medicine	Cases of decreased clearance in renal impairment 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	Risk factors for acute and chronic kidney failure include advanced age, diabetes, high blood pressure, heart disease, kidney disease, and unhealthy lifestyles (Mayo Clinic 2012a, 2014).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2, 4.4 and 5.2. • PL Section 2. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Important Identified Risk: Decreased Clearance in Hepatic Impairment

Evidence for linking the risk to the medicine	Cases of decreased clearance in hepatic impairment 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	Risk factors of acute liver failure include acetaminophen overdose, certain prescription medications (such as antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants), certain herbal supplements, toxins, autoimmune disease, diseases of the veins in the liver, and cancer (that begins in or spreads to the liver) (Mayo Clinic 2011a).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2, 4.4 and 5.2. • PL Section 2. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Important Potential Risk: Low Birth Weight	
Evidence for linking the risk to the medicine	Cases of low birth weight 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 low birth weight include genetic factors and environmental factors such as socio-economic 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 Bernabe 2004). Maternal seizures and antiepileptic drug polytherapy have also been associated with poor fetal growth (Hernàndez-Díaz 2017).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.3, 4.4, 4.6 and 4.8. • PL Section 2. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Important Potential Risk: Premature Delivery	
Evidence for linking the risk to the medicine	Cases of premature delivery have been reported in association with TOPIMAX in the postmarketing setting, and information related to this is described in the current prescribing information for TOPIMAX.
Risk factors and risk groups	There are several risk factors for preterm labor and birth, including prior preterm labor or delivery (Ekwo 1992), being pregnant with twins, triplets, or more, or the use of reproductive technology (Gardner 1995) and certain abnormalities of the reproductive organs. In addition, certain medical conditions can increase the risk, including urinary tract infections, sexually transmitted infections, certain vaginal infections, high blood pressure, vaginal bleeding, certain fetal developmental abnormalities, being under- or overweight during pregnancy, short time period between pregnancies (less than 6 months between a birth and the beginning of the next pregnancy), placenta previa, being at risk of uterine rupture, diabetes, gestational diabetes, and blood clotting problems (NICHD 2017a). Other factors that may increase risk include; ethnicity (CDC 2013b), age of mother (<18 years or >35 years of age), certain lifestyle and environmental factors, lack of healthcare during pregnancy, smoking, drinking alcohol, use of illegal drugs, domestic violence, stress, long working hours with long periods of standing, and exposure to certain environmental pollutants (NICHD 2017a). Women with nonepilepsy indications for antiepileptic drugs (eg, depression, bipolar disorders) have been shown to be at a higher risk for preterm infants. Of women taking antiepileptic drugs in the North American Antiepileptic Drug pregnancy registry, the risk of premature labor and birth was higher in women on polytherapy and in women with seizures during pregnancy.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.3, 4.4, and 4.6. • PL Section 2. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Missing Information: Use of TOPIMAX in Neonatal Seizures	
Risk minimization measures	Routine risk minimization measures:

	• SmPC Section 4.1. • PL Section 1. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Missing Information: Exposure of Infants to TOPIMAX via Breastfeeding	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6. • PL Section 2. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

Missing Information: With Long-Term Treatment of Pediatric Patients, the Association Between Metabolic Acidosis and Nephrolithiasis, Bone Mineral Density Abnormalities, and Delayed Growth	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4. • Legal status: medicinal product restricted to medical prescription only. Additional risk minimization measures: • None.

II.C. Post-authorization Development Plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of TOPIMAX.

II.C.2. Other Studies in Post-authorization Development Plan

There are no studies required for TOPIMAX.