PART VI: SUMMARY OF RISK MANAGEMENT PLAN FOR TOPIMAX® (TOPIRAMATE)

Name of Marketing Authorization Holder or Applicant	Janssen Research and Development, L.L.C
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand names)	TOPIMAX (also known as TOPAMAX®, TOPAMAC®, EPITOMAX™

Data-lock point for this Module	18 Jan 2018
Version number when Module last updated	22 May 2018

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	• Acute myopia and secondary angle-closure glaucoma • Metabolic acidosis • Suicide/suicide ideation • Major congenital malformations with use during pregnancy • Hyperammonemia with or without encephalopathy with or without concomitant valproic acid •
Important potential risks	None
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 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: 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

Important Identified Risk: Suicide / Suicide Ideation	
	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 4.3, 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: 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 Potential Risks

None

Missing Information

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.