

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Topiramate**

**Topamax, Topimax, Epitamax, Topamac, Topamax Dispersible**

**MT/W/0002/pdWS/001**

<b>Rapporteur:</b>	Malta
<b>Start of the procedure (day 0):</b>	24/05/2010
<b>Date of this report:</b>	
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):</b>	02/08/2010
<b>Deadline for CMS's comments (day 85):</b>	17/08/2010
<b>Date re-start procedure (day 90):</b>	14/10/2010
<b>Deadline for CMS's comments (day 115):</b>	8/11/2010
<b>Finalisation procedure (day 120):</b>	13/11/2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See Section VI Topamax Topimax Epitomax Topamac Topamax Dispersible
INN (or common name) of the active substance(s):	Topiramate
MAH (s):	See Section VI Janssen-Cilag GmbH Janssen-Cilag A/S Janssen-Cilag AB Janssen-Cilag AS Janssen-Cilag BV Janssen-Cilag OY Janssen-Cilag NV Janssen-Cilag Limited Janssen-Cilag Kft. Janssen-Cilag International NV Janssen-Cilag Farmacêutica, Lda. UAB Johnson & Johnson Johnson & Johnson, s.r.o Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o. Janssen-Cilag s.r.o Janssen-Cilag SpA Janssen-Cilag S.A.  Janssen-Cilag Pharmaceutical S.A.C.I.  Janssen-Cilag Pharma GmbH
Pharmaco-therapeutic group (ATC Code):	N03AX : other anti-epileptics
Pharmaceutical form(s) and strength(s):	25mg, 50mg, 100mg, 200mg, 300mg, 400mg Film-coated Tablets 15mg, 25mg, 50mg Capsules 15mg, 25mg, 50mg Sprinkle capsules

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## List of Abbreviations

ADR	Adverse drug reaction
AED	Anti epileptic drug
ATC	Anatomical therapeutic code
CHMP	Committee for medicinal products for human use
CLCR	Creatinine clearance
C <sub>max</sub>	Maximum plasma concentration
CNS	Central nervous system
GABA	Gamma – amino butyric acid
LGS	Lennox- Gastaut syndrome
MAH	Marketing authorisation holder
MES	Maximal electric shock
PdWS	Paediatric work sharing
PD	Pharmacodynamic
PGTC	Primary generalized tonic clonic seizures
PL	Patient leaflet
POS	Partial onset seizures
SER	Spontaneous epileptic rat
SmPC	Summary of product characteristics
T <sub>max</sub>	Time at which highest drug concentration occurs

## I. EXECUTIVE SUMMARY

Since its introduction in the 1990s topiramate has been used effectively as monotherapy or as adjunctive therapy in various types of epilepsy.

Data packages were submitted by the marketing authorisation holders (MAHs) for paediatric work sharing (PdWS) in conformity with Article 45 of the Paediatric Regulation (EC) no 1901/2006 as amended.

A recent evaluation of topiramate product information was performed via the Article 30 harmonisation procedure, and a summary of the harmonised indication information as it pertains to the paediatric population was submitted together with additional applicable paediatric studies meeting the Article 45 criteria.

Topiramate has been shown to be effective and to be well tolerated. The benefit/risk ratio has been shown to be favourable when used in the approved indications. However, there are some potential safety concerns because of lack of sufficient safety studies in children.

Additional safety information should be included in the SmPC to make the prescriber more aware of the potential problems which may occur in children. The patient leaflet should also contain information regarding the symptoms of over-dosage.

In this Paediatric Work Sharing procedure SmPC changes are proposed in sections 4.4, 4.8 and 5.1. PL additions are proposed to include signs and symptoms of over-dosage.

## II. RECOMMENDATION

In connection with Paediatric Work Sharing (PdWS) according to Article 45 of the Paediatric Regulation (EC) No 1901/2006 as amended, basing on a review of the paediatric data submitted by the Marketing Authorisation Holder (MAH) regarding the treatment of epilepsy in children with topiramate, and after consultation of the literature regarding topiramate, it is recommended that in connection with the safety of children the following wording should be added to the currently approved SPC and PL as per track changes in attached SPC and PL.

### **SmPC Section 4.4 special warnings and precautions for use:**

i. After the third paragraph regarding adequate hydration of the current SmPC the following additional paragraph should be added under the heading of Oligohydrosis:

“Oligohydrosis (decreased sweating) has been reported in association with the use of topiramate. Decreased sweating and rise in body temperature may occur especially in young children exposed to high ambient temperature.”

ii. After the 1<sup>st</sup> sentence of the 4<sup>th</sup> paragraph of sub-heading Metabolic acidosis of the current SmPC the following wording should be inserted so that the 4<sup>th</sup> paragraph would read as follows:

Depending on underlying conditions, appropriate evaluation including measurement of serum bicarbonate levels is recommended with topiramate therapy. If signs or symptoms are present (e.g. Kussmaul’s deep breathing, dyspnoea, anorexia, nausea, vomiting, excessive tiredness, tachycardia or arrhythmia), indicative of metabolic acidosis, measurement of serum bicarbonate is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

iii. Impairment of cognitive function in adults on topiramate therapy has been reported in the literature. It is therefore recommended that topiramate SmPC Section 4.4 should contain the following information under the additional heading:

“Impairment of cognitive function

Cognitive impairment in epilepsy is multifactorial and may be due to the underlying aetiology, due to the epilepsy or due to the anti epileptic treatment. There have been reports in the literature of impairment of cognitive function in adults on topiramate therapy which required reduction in dosage or discontinuation of treatment. However, studies regarding cognitive outcomes in children treated with topiramate are insufficient and its effect in this regard still needs to be elucidated.”

### **SmPC Section 4.8 Undesirable effects**

Under 4.8 Undesirable effects under Paediatric population concerning the ADRs occurring more frequently ( $\geq 2$ -fold) in children than in adults in double-blind controlled studies It is recommended that these items be highlighted singly with bullets to better draw the attention of prescribers to the possibility of these effects in children as follows:

- *Decreased appetite*
- *Increased appetite*
- *Hyperchloraemic acidosis*
- *Hypokalaemia*
- *Abnormal behaviour*
- *Aggression*
- *Apathy*
- *Initial insomnia*
- *Suicidal ideation*
- *Disturbance in attention*
- *Lethargy*
- *Circadian rhythm sleep disorder*
- *Poor quality sleep*
- *Lacrimation increased*
- *Sinus bradycardia*
- *Feeling abnormal*
- *Gait disturbance*

Similarly under ADRs reported solely in children but not in adults in double-blind controlled studies include:

- *Eosinophilia*
- *Psychomotor hyperactivity*
- *Vertigo*
- *Vomiting*
- *Hyperthermia*
- *Pyrexia*
- *Learning disability*

## **SmPC Section 5.1 Pharmacodynamic properties**

It is recommended that after the last paragraph of this section in the current SmPC the following information should be added under the heading:

### Absence seizures

“The results of two studies (CAPSS-326 and TOPMAT-ABS-001) on absences showed that topiramate treatment did not reduce the frequency of absence seizures”.

## **Patient Leaflet**

This needs an addition to include the signs and symptoms of over dosage viz.:

“Signs and symptoms of over dosage may include convulsions, drowsiness, speech disturbances, double vision, impaired thinking, abnormal coordination, dulling of consciousness, low blood pressure, abdominal pain, agitation, dizziness and depression.

The PL should reflect the recommended undesirable effects as in the SmPC.

## **Formulation**

The applicant should be encouraged to develop a liquid age- appropriate formulation for easier administration and to ensure correct dosage during the titration period and during maintenance treatment in small children.

## **Further studies**

Due to the insufficient information regarding the potential effects of topiramate on cognitive function and growth in children the applicant should be encouraged to sponsor:

- i. Short term pharmacodynamic studies to address the effects of topiramate on cognitive function in children.
- ii. Long term prospective observational studies focussing on the possible effects of cognitive function and growth in children.

## **III. INTRODUCTION**

The MAH submitted 21 completed paediatric studies for topiramate, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for topiramate and that there is no consequential regulatory action.

However as a result of this Paediatric Worksharing procedure it was recommended that the SmPC and PL should contain additional safety information as indicated under Section II, Recommendations, of this report.

Since its introduction in the 90s topiramate has been used effectively for the control of seizures in childhood.

The data packages were submitted for paediatric work-sharing by the marketing authorisation holders (MAHs) under Article 45 of the Paediatric Regulation (EC) No 1901/2006 as amended. This submission concerns

topiramate film-coated tablets and hard capsules. Topiramate is effective in controlling certain forms of epilepsy including childhood seizures. A recent evaluation of topiramate product information was performed via the Article 30 harmonisation procedure, and a summary of the harmonised indication information as it pertains to the paediatric population was submitted.

The following text was accepted by the Committee for Medicinal Products for Human Use (CHMP) for the use of topiramate in monotherapy for epilepsy, and is present in the current SmPC:

*"Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures."*

The following harmonised indication for topiramate adjunctive therapy in POS with or without secondary generalization or PGTC seizures in adults and in the paediatric population, and for the treatment of seizures associated with LGS was also adopted by the CHMP, and is present in the current SmPC:

*"Adjunctive therapy in children aged 2 years and above, adolescents and adults 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."*

The company (J&JPRD) currently markets topiramate products as orally administered film-coated tablets and hard capsules. There is as yet no liquid paediatric formulation.

It is considered that the benefit/risk ratio for topiramate continues to be favourable in the approved indications. However, there are some concerns regarding lack of sufficient PD studies and lack of long term observational studies concerning the use of topiramate in young children. There are concerns regarding cognitive development in these young children and the potential effects on bone growth.

Bone growth during topiramate therapy should be monitored. Studies should also be encouraged regarding the possible effects of topiramate on cognitive development. As recommended by CHMP (CHMP/EWP/566/98/Rev.2) special attention should be given to the occurrence or exacerbation of CNS adverse events e.g. those involving cognition, thought processes, memory, lethargy, emotional and behavioural reactions, psychotic or depressive symptoms, suicidal behaviour/ideation, disturbances of gait, speech, coordination and nystagmus. This may present difficulties as observed effects have to be disentangled from those of any underlying condition and from the effects of any co-medication which may also affect cognitive development.

The MAH stated that the submitted paediatric studies do not influence the benefit-risk and that there is no consequential regulatory action. However, in connection with this PdWS procedure the Rapporteur recommends that the SmPC should contain some additional safety information as outlined under Recommendations.

## **4.1 – Therapeutic Indications**

### **Monotherapy for epilepsy**

*"Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures."*

### **Adjunctive therapy for epilepsy in children and adults**

*”Adjunctive therapy in children aged 2 years and above, adolescents and adults 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.”*

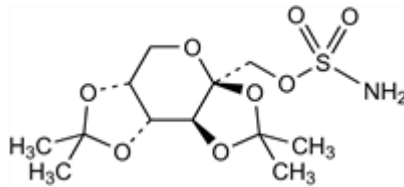
### **Prophylaxis of migraine**

*“Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.”*

## **IV. SCIENTIFIC DISCUSSION**

### **Information on the pharmaceutical formulation used in the clinical study(ies)**

Topiramate is a sulfamate-substituted monosaccharide. Topiramate enhances  $\gamma$ -aminobutyrate-activated chloride channels and inhibits excitatory neurotransmission, through actions on kainate subtypes of glutamate receptors and  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. It is also an inhibitor of some isozymes of carbonic anhydrase.



Chemical Structure of Topiramate

After oral administration of single doses, peak serum levels are attained within 2 to 4 hours. When taken with food absorption is delayed. Steady-state plasma concentrations of topiramate increase linearly with the dose. Serum protein binding is about 15%. Elimination half-life is 20 to 30 hours. Topiramate is mainly excreted unchanged in the urine but a proportion is metabolized by oxidation. Phenytoin and carbamazepine induce the metabolism of topiramate and markedly decrease the serum levels. Valproate may also lower topiramate concentrations but to a much lesser extent.

### **Pharmacodynamic properties**

Pharmacotherapeutic group: other anti-epileptics, anti-migraine preparations, ATC code: N03AX11

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its anti-seizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate. Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which  $\gamma$ -aminobutyrate (GABA) activated GABA receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

### **Pharmacokinetic properties**

The film-coated tablet and hard capsule formulations are bioequivalent. The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites. Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

### **Absorption**

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C<sub>max</sub>) of 1.5 µg/ml was achieved within 2 to 3 hours (T<sub>max</sub>).

### **Distribution**

Generally, 13 to 17% of topiramate is bound to plasma protein.

### **Metabolism**

Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes.

### **Elimination**

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of <sup>14</sup>C-topiramate was excreted unchanged in the urine within four days.

Concomitant multiple-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR ≤ 60 ml/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. Topiramate is effectively removed from plasma by haemodialysis.

Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

### Paediatric population (pharmacokinetics, up to 12 years of age)

The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme-inducing anti-epileptic drugs decrease the steady state plasma concentrations.

A liquid paediatric formulation is not yet available.

### **Non-clinical aspects**

In animal studies, topiramate exhibits anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests and is effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by

global ischemia. Topiramate is only weakly effective in blocking clonic seizures induced by the GABAA receptor antagonist, pentylentetrazole.

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

The film-coated tablet and hard capsule formulations are bioequivalent. The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

### **Clinical aspects**

In connection with this PdWS procedure the applicant submitted 21 reports to support the efficacy and safety of topiramate in studies which included children as are summarised in the following Table 1.

**Table 1: Clinical Studies Conducted in Paediatric Subjects but Not Intended as Pivotal Studies in Support of an Indication**

Study	Design and Dosage	Number of Patients
<b>Monotherapy in Epilepsy</b>		
<u>Open-Label, Single-Arm, Phase 3b/4 Study</u>		
PRI/TOP-INT-51	International, multicentre, open-label, dosage optimisation study as monotherapy of subjects >2 years of age with recently diagnosed epilepsy. Seven months of mandatory treatment with optional treatment up to 13 months.  TPM initiated at 0.5 mg/kg/day for children (≤16 yrs of age) and increased by 0.5 mg/kg/day in weekly increments over 6 weeks to the initial target dosage (3 mg/kg/day). Dose adjusted according to response (maximum 9 mg/kg/day).	Treated in double-blind phase: 692 Age ≤16 yrs, n=187  Treated in extension phase: 554
<u>Open-Label, Non-interventional Study</u>		
TOP-EPY-0001	Multicentre, open-label, non-interventional, prospective, 12-week study of subjects (≥6 yrs of age) previously treated with carbamazepine, oxcarbazepine, valproic acid or phenytoin switched to TPM monotherapy.  Regimen left to physician's decision based on recommendation in the current SmPC. TPM dosages for ITT group: Initial: median, 25 mg/day; range, 12.5-200 mg/day Maximal dosage: mean, 135 mg/day; range, 50-400 mg/day Maximal dosage at endpoint: median 100 mg/day; range, 25-500 mg/day	Treated: 446 (median age 44 yrs, range 7-91 yrs; ITT population with n =407)
<u>Open-Label, Non-interventional Study</u>		
TOP-GER-11	Multicentre, non-interventional, monotherapy 12- month study of subjects previously enrolled in TOP-GER-5 (a Phase 4 study of patients with newly diagnosed epilepsy and new treatment with TPM) or observed in TOP-GER-12 (a 30-week non-interventional, study of TPM in patients with previously untreated or unsuccessfully treated epilepsy).  Subjects received TPM as first-line or add-on therapy; 92.9% had transitioned to monotherapy within 6 weeks of starting TOP-GER-5 or TOP-GER-12. Average TPM dosages for ITT group by end of study: mean, 132 mg/day; range, 25- 400 mg/day	Treated: 114 (mean age 43 yrs, range 16-78 yrs) TOP-GER-5, n=62 TOP-GER-12, n=52
<u>Open-Label, Non-interventional Study</u>		
TOP-GER-12	Multicentre, non-interventional study of patients ≥ 12 years of age with epilepsy, 7 months of treatment  No dosage data available	Treated: 250

**Table 1: Clinical Studies Conducted in Paediatric Subjects but Not Intended as Pivotal Studies in Support of an Indication (continued)**

Study	Design and Dosage	Number of Patients
<b>Adjunctive Therapy in Epilepsy</b>		
<u>Open-Label, Non-interventional Study</u>		
JC-AWB-0009	Open-label, multicentre, 6-month study as adjunctive therapy in subjects ( $\leq 12$ yrs of age) with a confirmed diagnosis of epilepsy, who had received prior monotherapy without success with an AED other than topiramate before the start of the noninterventional study.  Of the patients who achieved the maintenance phase, the topiramate dosage was $\leq 100$ mg/day for 26 patients. 54 patients received a dosage between 100 and 200 mg/day; 27 patients received a dosage between 200 and 300 mg/day; 8 patients received a dosage between 300 and 400 mg/day.	Treated: 167 (mean age 43.8 years, range 7-81 years).
<u>Open-Label, Single-Arm, Phase 3 Study</u>		
TOPMAT-EPAJ-111 (PRI/TOP-INT-1)	Open-label, multicentre, 10 month study as adjunctive therapy in subjects ( $\geq 12$ yrs of age) with POS with or without secondary generalisation.  Topiramate initiated at 50 mg/day and increased in 50 mg/day weekly increments until achieving either the maximum effective dosage or maximum tolerated dosage, whichever came first. Total daily dosage was not to exceed 1,600 mg/day.	Treated: 1174 Age 10-16 yrs, n=77
<u>Open-Label, Single-Arm, Phase 3b Study</u>		
TOPMAT-EPPD-002	Open-label, multicentre study of adjunctive therapy in subjects (1-18 yrs of age; $\geq 11$ kg) with inadequately controlled POS (with or without secondarily generalised seizures); seizures associated with LGS; and generalised tonic-clonic, myoclonic, or absence seizures.  Topiramate initiated at 1 mg/kg/day and subsequently titrated upward to the minimum effective dosage, the maximum tolerated dosage or the maximum allowed dosage (24 mg/kg/day).	Treated in core phase: 554 Treated in extension phase: 195
<u>Open-Label, Double-Arm, Non-interventional Study</u>		
TOP-EPY-401	Single centre, non-interventional, 12-week, monotherapy study of TPM-naïve subjects ( $\geq 12$ yrs of age).  TPM initiated at 50 mg/day and titrated according to clinical situation: Rapid titration, 100 mg/day attempted at 3 days; Normal titration, 100 mg/day attempted at 12 days	Treated: 50 (median age 37 yrs, range 17-67 yrs) Rapid titration group, n=29 Normal titration group, n=21

**Table 1: Clinical Studies Conducted in Paediatric Subjects but Not Intended as Pivotal Studies in Support of an Indication (continued)**

Study	Design and Dosage	Number of Patients
<b>Adjunctive Therapy in Epilepsy (continued)</b>		
<u>Open-Label, Non-interventional Study</u>		
TOP-GER-10	<p>Multicentre, non-interventional, 7-month study of TPM as first-line adjunctive therapy in subjects (<math>\geq 12</math> yrs of age) with epilepsy.</p> <p>Regimen left to physician's decision based on recommendation in the current SmPC. Subjects received TPM as first-line or add-on therapy, 6.3% of subjects were started on TPM monotherapy and 35% discontinued a concomitant AED during the study.</p> <p>Average TPM dosages for ITT group by end of study: mean, 118 mg/day; median, 98 mg/day; range, 25- 451 mg/day</p>	<p>Treated: 240 (mean age 42 yrs, range 12-89 yrs for efficacy population with n =239)</p> <p>N=12 were <math>\leq 18</math> years of age</p>
<b>Monotherapy or Adjunctive Therapy in Epilepsy</b>		
<u>Open-Label, Non-interventional Study</u>		
JWC-AWB-0003	<p>Prospective, multicentre, open-label study of topiramate as monotherapy in patients 2 years of age and older, who suffer from epilepsy with focal seizures (with or without secondary generalisation), PGTC seizures, or LGS, and currently under standard treatment with one or more AEDs.</p> <p>Of the 54 patients with available dosage data, 25 received topiramate monotherapy dosages between 75 mg/day and 450 mg/day (average dosage: 205 mg/day), and 29 patients received topiramate add-on therapy at dosages between 125 mg/day and 600 mg/day (average dosage: 255 mg/day).</p>	<p>Treated: 60 (mean age 39 years, range 1-72 years).</p>
<u>Open-Label, Single Arm Study</u>		
PRI/TOP-ITA-3	<p>Multicentre, open-label, prospective, 6-month study in children (1-18 yrs of age) with epilepsy unsuccessfully controlled by one AED.</p> <p>Topiramate was titrated by 0.5 mg/kg/day in weekly increments (titrated by 1 mg/kg/day once above 4 mg/kg/day) until minimum effective dosage, maximum tolerated dosage or the maximum allowed dosage (24 mg/kg/day). Patients had free option to transition to monotherapy, with 11 patients doing so during the study. Mean final TPM dosage, 5.9 mg/kg/day.</p>	<p>Treated: 57 (mean age 6.9 yrs, 19% <math>\leq 2</math> yrs)</p>
<u>Open-Label, Non-interventional Study</u>		
TOPMAT-EPP-401	<p>Multicentre, non-interventional study of children (6-16 yrs of age) with epilepsy.</p> <p>Patients received TPM as first-line or add-on therapy, 32 patients transitioned to monotherapy during the study. Mean TPM dosage at end of study, 2.99 mg/kg/day</p>	<p>Treated: 54</p>

**Table 1: Clinical Studies Conducted in Paediatric Subjects but Not Intended as Pivotal Studies in Support of an Indication (continued)**

Study	Design and Dosage	Number of Patients
<b>Monotherapy or Adjunctive Therapy in Epilepsy (continued)</b>		
<u>Open-Label, Non-interventional Study</u>		
TOP-GER-7	<p>Non-interventional 4-month study of children age 12 and above and adults who were being treated with topiramate for the first time for epilepsy.</p> <p>Patients received TPM as first-line or add-on therapy. Patients who received topiramate monotherapy (n = 4) were treated with an average of 105.2 mg/day (12.5-150 mg/day). Patients who received topiramate as add-on therapy were treated with an average of 143.3 mg/day (25-200 mg/day).</p>	Treated: 19 (mean age 43 years, range 12-93 years).
<u>Open-Label, Non-interventional Study</u>		
TOP-GER-8	<p>Multicentre, national, non-interventional 6-month study of subjects (2-16 yrs of age) with epilepsy.</p> <p>Regimen left to physician's decision based on recommendation in the current SmPC.</p> <p>TPM monotherapy received by 77 subjects: mean dosage, 3.25 mg/kg/day; range, 0.7-9.2 mg/kg/day. TPM adjunctive therapy received by 95 subjects: mean dosage, 4.5 mg/kg/day; range, 1.0-35.4 mg/kg/day.</p>	<p>Treated: 174 Age &lt;6 yrs, n=50 Age 6-16 yrs, n=122 Age unknown, n=2</p>
<u>Open-Label, Non-interventional Study</u>		
TOPMAT-EPY-402 (TOP-GER-T3)	<p>Single centre, open-label, prospective, 3-month study in children with epilepsy unsuccessfully controlled by one AED.</p> <p>Daily dosage was calculated to body weight: the initial dosage averaged 1.1 mg/kg/day, the maximum dosage was 4.6 mg/kg/day, and the last dosage at the end of the study averaged 3.3 mg/kg/day, with a maximum dosage of 6.7 mg/kg/day and a minimum dosage of 0.5 mg/kg/day.</p>	Treated :19 (mean age 4.4 years, range 2-12 years).
<u>Open-Label, Non-interventional Study</u>		
TOPMAT-EPY-403	<p>Multicentre, open-label, prospective, 5-month study in children ≥ 12 years of age and adults with recently diagnosed or refractory epilepsy, transitioning from valproic acid to TPM. Patients could continue existing or receive other AEDs at the discretion of the treating physician.</p> <p>The mean dosage at study end was 144 mg/day overall and among patients who achieved monotherapy (n=103).</p>	Treated:147 (mean age 41 years, range 10-90).

**Table 1: Clinical Studies Conducted in Paediatric Subjects but Not Intended as Pivotal Studies in Support of an Indication (continued)**

Study	Design and Dosage	Number of Patients
<b>Absence Seizures</b>		
<u>Open-Label, Single-Arm, Phase 2 Study</u>		
CAPSS-326	Open-label, single-arm, multicentre, 24-week titration study of children (ages 4-9 yrs) with absence seizures.  Topiramate initiated at 15 mg/day (subjects weighing 15-24 kg) or 25 mg/day ( $\geq 25$ kg) and titrated upward at weekly intervals, depending on response, to a maximum of the lesser of 9 mg/kg/day or 400 mg/day.	Treated: 12 (range 4-9 yrs of age)
<u>Open-Label, Single-Arm, Phase 2 Study</u>		
TOPMAT-ABS-001	Open-label, single-arm, single-centre, 6-week titration study of children (ages 4-11 yrs) with absence seizures. Subjects completing core phase were enrolled in the extension phase at the investigator's discretion.  Topiramate initiated at 1 mg/kg/day, increased twice weekly by 1 mg/kg/day over 6 weeks to a target of 12 mg/kg/day.	Treated: 5 (mean age 8.6 years, range 6-11 yrs of age)
<b>Infantile Spasms</b>		
<u>Open-Label, Single-Arm, Phase 1 Study</u>		
TOPMAT-EPIS-003	Open-label, single-arm, multicentre, 12-week (6-week titration period, 6-week stabilisation period) study in subjects (age 1-36 months) with infantile spasms.  Topiramate initiated at 15 mg/day and increased 3 mg/kg/day every 3 days until infantile spasms were absent for 7 days, the maximum tolerated dosage, or the maximum allowable dosage (50 mg/kg/day) was reached. Target dosage was 18 mg/kg/day.	Treated: 21 (mean 8.6 months, range = 0.8 to 25.8 months)
<b>Migraine Prophylaxis</b>		
<u>Double-Blind, Placebo-Controlled, Phase 3 Study</u>		
TOPMAT-MIG-3006	Randomised, double-blind, placebo-controlled, parallel-group, 3-arm, fixed dose-ranging 18-week study of subjects (age 12-17 yrs) with episodic migraine headaches.  Placebo Topiramate titrated up over a 4-week period until the final target dosage (50 or 100 mg/day) or maximum dosage tolerated had been achieved.	Treated: 103 PLA, n=33 TPM 50 mg/day, n=35 TPM 100 mg/day, n=35
<b>Bipolar I Disorder</b>		
<u>Double-Blind, Placebo-Controlled, Phase 3 Study</u>		
TOPMAT-PDMD-009	Randomised, double-blind, multicenter, placebo-controlled 4-week study of subjects (range 13-17 yrs of age) with bipolar I disorder, with an optional 6-month open-label extension.  Placebo Topiramate target daily dosage of 400 mg (based on tolerability) twice daily in a blinded fashion for up to 28 days.	Treated in double-blind phase: 56 PLA, n=27 TPM 400 mg/day, n=29  Treated in extension phase: 43 PLA, n=23 TPM 400 mg/day, n=20

AED = antiepileptic drug; ITT = Intent-to-Treat; LGS = Lennox-Gastaut syndrome; n = size of a subsample; PLA = placebo; POS = partial-onset seizures; PGTC = partial generalized tonic clonic seizures; SmPC = Summary of Product Characteristics; TPM = topiramate; yr = year

## Discussion on clinical aspects

The above mentioned study reports regarding the use of topiramate in the treatment of epilepsy which were submitted by the applicant for paediatric work-sharing according to Article 45 of the paediatric Regulation 1901/2006 as amended were reviewed in terms of efficacy and safety and recommendations for updating of the SmPC.

The studies referred to by the Applicant in connection with a recent evaluation of topiramate was performed via the Article 30 harmonisation procedure viz. TOPMAT-EPMN-106 which were carried out in newly diagnosed patients. These included 300 patients aged between 6 and 16 years of age. The results of these studies and of study TOPMAT-EPMN-104 which were accepted by the CHMP and were the basis for one of the indications for use of topiramate as monotherapy in the current SPC. Further supporting studies as per Table 1 were submitted in connection with this Paediatric Work-sharing procedure in terms of Art 45 of the Paediatric Regulation have shown that topiramate is significantly effective in reducing the number of seizures when used within the paediatric indications of the SmPC.

The use of topiramate in children within the authorised indications is clearly effective. It has also been shown that adverse effects are within its known safety profile and that adverse effects are moderate. However, there are some safety concerns regarding the use of topiramate in childhood epilepsy. Some patients seem to be susceptible to cognitive decline which may sometimes be attributed to the epilepsy and/or to co-medication when this cognitive change could in fact be due to the effect of topiramate itself. Few data are available defining adverse effects in children because clinical trials for paediatric use of AEDs are generally small and focussed on efficacy. Most of the studies submitted included children among the population studied but did not exclusively concern children. This may result in the relatively small number of children being diluted by the large number of adult patients with the possibility that the negative impact of drugs may be overlooked in the growing child. In this regard some concerns about the effects of topiramate on cognitive development and growth remain.

Possible effects of topiramate have to be disentangled from what may be clinical manifestations of the underlying condition causing the seizures, the nature of seizures and their frequency and from the effects of any co-medication. Carers of children and their clinicians should be informed of the possibilities so that they can be alert for possible cognitive changes. This highlights the need for more information in the SmPC and the need for regular supervision during treatment with topiramate. Anti epileptic drugs (AEDs) have distinct effects on brain function. Many other factors besides AEDs may be involved in cognitive function including the underlying condition and the type, severity and frequency of seizures particularly, for patients with long term uncontrolled seizures. Cognitive effects typically include diminished attention, executive function, intelligence, language skills, memory and processing speed.

Because of the different metabolism and stage of maturation at different ages and because of the different and pathologies in children it can be difficult to extrapolate safety data from that of adults. This highlights the necessity having *ad hoc* clinical studies regarding the use of topiramate in children.

Although topiramate is being increasingly used in young children and its uptake has been rapid, specific studies regarding its use in children have been insufficient in number and of short duration.

By nature children are more vulnerable than adults. They may not be aware of adverse drug reactions or adverse effects especially those involving growth and cognitive effects. Specific long term studies in children are required especially regarding the potential effects of topiramate on cognitive development.

As a result of this PdWS procedure some additional safety information is recommended to be added to the current SPC under Sections 4.4, 4.8 and 5.1 as indicated under Section II of this report. The incorporation of these changes in the SPC and PL will require a type II variation.

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **Overall conclusion**

The above mentioned study reports regarding the use of topiramate in the treatment of epilepsy which were submitted by the applicant for paediatric work-sharing according to Article 45 of the paediatric Regulation 1901/2006 as amended. These were reviewed in terms of efficacy and safety and updating of the SmPC.

The use of topiramate in children within the approved indications is effective and well tolerated. However, the SmPC and PL need to be updated by the inclusion of additional information regarding safety and efficacy as indicated in the Recommendations. For these reasons the MAH is requested to make a type II Variation in the SmPC and PL.

### **Recommendation**

A Type II variation of the SmPC in Sections 4.4, 4.8 and 5.1 as indicated at the beginning of this report under **II Recommendations** is requested from the MAH by **13<sup>th</sup> April 2011**.

## **VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED**

*The list can be taken from the spreadsheet compiled from the EMA.*