

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Topiramaat Apotex 25/50/100/200 mg film-coated tablets
Apotex Europe B.V., the Netherlands

topiramate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1231/001-004/MR
Registration number in the Netherlands: RVG 33204-33207

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Pharmacotherapeutic group:	other antiepileptic agents
ATC code:	N03AX11
Route of administration:	oral
Therapeutic indication:	<i>adults, adolescents and children aged over 6 years: partial seizures with or without secondary generalised seizures, and generalised tonic-clonic seizures (monotherapy); children aged 2 years and above, adolescents and adults: partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures, seizures associated with Lennox-Gastaut syndrome (adjunctive therapy); adults: prophylaxis of migraine headache after careful evaluation of possible alternative treatment options</i>
Prescription status:	prescription only
Date of first authorisation in NL:	31 August 2006
Concerned Member States:	Mutual recognition procedure with CZ, IT, PL, and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Topiramaat Apotex 25/50/100/200 mg film-coated tablets, from Apotex Europe B.V. The date of authorisation was on 31 August 2006 in the Netherlands.

The product is indicated:

- as monotherapy in adults, adolescents and children aged over 6 years of age with partial seizures with or without secondary generalised seizures, and generalised tonic-clonic seizures.
- as 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.
- as prophylaxis for migraine headache in adults after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.

A comprehensive description of the indications and posology is given in the SPC.

Topiramate is an antiepileptic agent classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity. Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels. Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainite/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This effect is not thought to be a major component of topiramate antiepileptic activity.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Topamax 25/50/100/200 mg film-coated tablets (NL license RVG 24165-24168) which have been registered in the United Kingdom by Janssen-Cilag since 1995 (original product). In the Netherlands, Topamax 25/50/100/200 mg film-coated tablets have been registered since 1999. In addition, reference is made to Topamax authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Topamax 200 mg film-coated tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

Topiramate is not described in the European Pharmacopoeia (Ph.Eur.*). However an in-process revision of a USP monograph is available. The drug substance is a white or almost white powder. It is soluble in water and methanol. Topiramate possesses 4 asymmetric carbon atoms; all in the D-fructose moiety. Optical activity is controlled by a requirement in the specification. No polymorphs are known.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture

Topiramate is prepared from a commercially available starting material via a one-step synthesis and subsequent crystallization processes. Adequate certificates of analysis of the starting materials and reagents have been provided. The drug substance has been adequately characterized.

Specification

The drug substance specification is in compliance with the Ph.Eur. monograph Substances for pharmaceutical use and with the USP draft monograph, with additional requirements for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various ICH guidelines.

Stability

Stability data has been obtained during storage at 2-8°C, 25°C/60% RH, 30°C/65%RH and 40°C/75% RH. The drug substance was packaged in the commercial packaging, i.e. double LDPE bag. The substance is unstable at 40°C. At first the DMF-holder claimed a retest period at 2-8°C. The claimed retest period has however been adapted to 9 months stored below 25°C. Based on the available stability data, a re-test period of 18 months, stored below 25°C, can be granted. The substance should be stored in the original package for protection against light.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition

Each tablet contains 25 mg, 50 mg, 100 mg or 200 mg topiramate.

The 25 mg tablets are white and round and have an inscription "APO" on one side and "TP 25" on the other. The 50 mg tablets are light yellow and round and have an inscription "APO" on one side and "TP 50" on the other.

The 100 mg tablets are mustard-coloured and round and have an inscription "APO" on one side and "TP 100" on the other.

The 200 mg are reddish brown and round and have an inscription "APO" on one side and "TP 200" on the other.

The film-coated tablets are packed in an aluminium/aluminium blister pack or a HDPE bottle with PP cover and a desiccant.

The excipients are:

Tablet core: methylcellulose (E461), croscarmellose sodium (E468), magnesium stearate (E470b), and silica, colloidal anhydrous (E551).

Film coating: hypromellose (E464), hydroxypropylcellulose (463), macrogol, titanium dioxide (E171), as colouring agent in the 50 mg and 100 mg tablets: ferric oxide yellow (E172), as colouring agent in the 200 mg tablets: ferric oxide red (E172).

The tablets are dose proportional concerning active substance and excipients.

Pharmaceutical development

The development of the products is satisfactory performed and explained. The excipients used are common in the manufacture of tablets and some are also present in the innovator product. Where relevant the excipients comply with Ph.Eur. or the NF. The specifications of the excipients are acceptable. The packaging materials (Al/Al blisters and HDPE bottles) are usual and suitable for the product at issue.

Dissolution profiles show that the products at issue are pharmaceutically equivalent to the reference product. Comparative dissolution profiles of Topamax 200 mg, 100 mg and 25 mg from NL versus the corresponding brand tablets from several European countries (UK, DK, SE, FR, CZ, NO, PL, FI, IT and NL), have also been submitted. It is demonstrated that for all three tablet strength dissolution profiles are similar, they dissolve fast; there are also no significant differences between the UK products which have been used in the bioequivalence study, and the NL products. The MAH concludes that a single-point dissolution requirement is sufficient for this product. The limit proposed is $Q \geq 75\%$ in 30 min. The proposed dissolution method and the proposed limit are deemed acceptable.

Manufacturing process

The tablets are prepared from a common granulate. The granulate is compressed and subsequently coated. Each tablet strength has a different colour. The manufacturing process has been sufficiently described. Content uniformity of the blend has been demonstrated. Process validation data on the product have been presented for 3 pilot scale batches (at least 10% of the intended commercial scale) of each strength in accordance with the relevant European guidelines.

Product specification

The product specification for the powder includes tests for appearance, identification, assay, degradation, tablet weight, microbiological requirements and uniformity of dosage units. The proposed tests and requirements are acceptable. Batch analysis data have been provided on 3 pilot batches of each strength. Compliance with the release requirements is demonstrated.

Stability tests on the finished product

Three batches of each tablet strength have been stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. An increase in degradation is seen at accelerated conditions leading to impurity content outside the specification after 6 months of storage. Instability has also been observed after 18 months at intermediate conditions. The product is shown to be stable at long term conditions. The storage conditions are therefore limited to "store below 25°C". A mass imbalance is observed at 40°C/75%RH. This is probably due to formation of volatile impurities. The claimed shelf-life of 24 months can be granted. The storage conditions are 'Store below 25°C'. The product should be stored in the original package for protection against moisture.

The MAH has committed to place the first three commercial production batches on long-term and accelerated stability program. Results covering the whole shelf-life should be sent in when available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A valid TSE certificate is provided for magnesium stearate, which is of animal origin. The source of magnesium stearate has been changed into one of vegetable origin by a post-approval type IA variation. See "steps taken after the finalisation of the finished product" table on page 10, variation NL/H/1231/001-004/IA/002.

II.2 Non-clinical aspects

This product is a generic formulation of Topamax, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of topiramate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Topiramate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Topiramaat Apotex 200 mg film-coated tablets (Apotex Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the British reference product Topamax 200 mg film-coated tablets (Janssen-Cilag, UK).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states (UK, DK, SE, FR, CZ, NO, PL, FI, IT and NL), see also *Quality aspects - pharmaceutical development*.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

A single dose, blinded, randomised, two-way, cross-over bioequivalence study was carried out under fasted conditions in 24 (12 males, 12 females) healthy volunteers, aged 22-44 years, with BMI 20-28. Each subject received a single dose (200 mg) of one of the 2 topiramate formulations. The tablets were administered with 240 ml of water. Water could be taken *ad libitum* four hours after intake of the tablets. There were 2 dosing periods, separated by a washout period of 4 weeks. Blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 96, 144, 192 and 240 hours after administration of the products.

Eight subjects were excluded from study before entering study period II, seven because of side effects and one for personal reasons. Data of the 16 remaining subjects were eligible for pharmacokinetic analysis.

The analytical method is adequate validated and considered acceptable for analysis of the plasma samples. The long term stability data are covering the storage period of the plasma samples.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ (median, range)) of topiramate under fasted conditions.

Treatment N=16	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	155.4 $\pm$ 28.0	160.3 $\pm$ 29.0	4.2 $\pm$ 0.9	1.33 (0.25-4)	49.6 $\pm$ 18.8
Reference	154.0 $\pm$ 25.8	158.5 $\pm$ 25.7	4.3 $\pm$ 0.9	1.33 (0.5-5)	47.2 $\pm$ 17.7
*Ratio (90% CI)	1.01 (0.98-1.03)	1.01 (0.98-1.03)	0.97 (0.90-1.03)	---	---
CV (%)	3.2	4.5	11.0	---	---

AUC_{0-∞}	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
t_{1/2}	half-life

**ln-transformed values*

In the protocol, it was stated that 17 subjects would be recommended to meet the 80-125% CI limits with a statistical power of at least 80%. Because of the considerable number of eight withdrawals in this study, data from only 16 subjects were available for statistical analysis. Considering the low intra-individual variability (4-11%) of the ratio between the test and reference product, this number is considered acceptable.

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of topiramate under fasted conditions, it can be concluded that Topiramaat Apotex 200 mg film-coated tablets and Topamax 200 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 25, 50, and the 100 mg tablets are dose-proportional with the 200 mg tablet. The tablets have been manufactured by the same manufacturing process and manufacturer. In addition, topiramate shows linear pharmacokinetics. Considering the linear pharmacokinetics of topiramate in the therapeutic range, the results obtained for the 200 mg tablet can be extrapolated to the other strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Topiramate was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of topiramate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The SPC is in line with the SPC of the innovator product in the Netherlands.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each.

Fifteen questions were prepared to test for the understandability and the applicability of important information in the PIL. The findability was tested in all the fifteen questions. Questions were generated from important sections in the PIL, which were related to the safe and effective use of topiramate.

Between the two test rounds no changes to the PIL were made.

The test shows that the test persons had difficulties in finding and understanding the information regarding the contraindication for allergy to the active substance. This is however fixed information in terms of place in the PIL and content according to the QRD-template. For all other questions the understandability, applicability and findability was considered acceptable.

The Topiramate readability test has demonstrated that several aspects of the PIL can be improved. In line with results of the readability test and comments of the test persons, a number of suggestions for improvement are proposed in the readability test report:

- 1) Question 11, section 2, first sub header: The sub header can be made more prominent by printing the word “niet” in capitals. This suggested adaptation will improve both the findability and the understandability of the information.
- 2) Text with underlined style can be changed in bold style.
- 3) It is suggested to use portrait page setup instead of landscape page setup for the leaflet when the leaflet is printed.

Since the changes were relatively minor, a re-test of the adapted PIL was not considered necessary. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Topiramaat Apotex 25/50/100/200 mg film-coated tablets have a proven chemical-pharmaceutical quality are a generic form of Topamax film-coated tablets. Topamax is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the innovator product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Topiramaat Apotex was authorised in the Netherlands on 31 August 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Topiramaat Apotex 25/50/100/200 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 17 December 2007.

The MAH will submit PSURs every 3 years, based on the Data Lock Point of the innovator product Topamax (31 January 2009). The first PSUR will cover the period from 17 December 2007 until 31 January 2009.

The date for the first renewal will be 30 September 2009.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- Current stability data is 18-24 months at 25°/60% RH packaged in cold form blisters and HDPE bottles. The MAH has committed to continue stability studies on these batches to 36 months.
- The MAH has committed to place the first three commercial production batches on long-term and accelerated stability program. Results covering the whole shelf-life should be sent in when available. Every year thereafter, one production batch will be added to the long-term stability program.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _½	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Adaptation of SPC section 4.4 and PIL section 2 to suicidal warning for anti-epileptics	NL/H/1231/001-004/II/001	II	5-11-2008	17-12-2008	Approval	N
Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material. The excipient magnesium stearate is of vegetable origin.	NL/H/1231/001-004/IA/002	IA	22-1-2009	16-2-2009	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/1231/001-004/IA/003	IA	25-2-2009	11-3-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/1231/001-004/IA/004	IA	25-2-2009	11-3-2009	Approval	N
Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance. Minor change to an approved test procedure.	NL/H/1231/001-004/IA/005	IA	25-2-2009	11-3-2009	Approval	N
Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance. Minor change to an approved test procedure.	NL/H/1231/001-004/IA/006	IA	25-2-2009	11-3-2009	Approval	N
Change in batch size of the finished product.	NL/H/1231/001-004/IA/007	IA	25-2-2009	11-3-2009	Approval	N
Renewal of the marketing authorization.	NL/H/1231/001-004/R/001	Renewal	27-4-2009	26-6-2009	Approval	Y, Annex I
Change in the Summary of Product Characteristics and Package Leaflet following a referral procedure in accordance with Article 30 of Directive 2001/83/EC for the reference product, Topamax.	NL/H/1231/001-004/IB/008	IB	18-8-2010	17-9-2010	Approval	N
Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH.	NL/H/1231/001-004/IB/009	IB	24-5-2011	24-6-2011	Approval	N

Annex I – renewal marketing authorization (NL/H/1231/001-004/R/001)

I.1 Introduction

The products contain the active ingredient topiramate, which is an antiepileptic and migraine prophylaxis. Topiramate Apotex 25/50/100/200 mg film-coated tablets have the following indications:

Adults and adolescents aged 12 years and older: Adjuvant therapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Adults and adolescents aged 12 years and older: Monotherapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Adults: second-line therapy for migraine prophylaxis.

The products are registered through the Mutual Recognition Procedure with the Netherlands acting as Reference Member State.

The MAH has submitted pharmacovigilance documents in scope of renewal of the Marketing Authorisations. It concerns the following documents:

- PSUR covering the period 31 January 2006 to 30 January 2009, dated 27 March 2009.
- Clinical Expert Statement, dated 27 March 2009.

The MAH did not submit a proposal for a SPC update.

RMS' comment: The DLP within the EU PSUR harmonisation project is January 2009 (Sweden=pRMS). The MAH should submit the next PSUR, covering the period January 2009 – January 2012, within 60 days after DLP.

I.2 Data review

World wide marketing authorisation status

At data lock point topiramate was registered in 11 countries worldwide and currently on the market in Canada and Poland. So, the product under review is not on the market in the Netherlands. The IBD is 19 April 2006.

Update of regulatory authority or MAH actions taken for safety reasons

The MAH indicates that in December 2008 the FDA completed an analysis of reports of suicidality from placebo-controlled clinical studies with drugs to treat epilepsy as well as psychiatric disorders and other conditions. The outcome of the analysis was that patients receiving antiepileptic drugs had about twice the risk of suicidal behaviour or ideation as compared to patients receiving placebo. Based on this analysis, the FDA required all MAHs of antiepileptic/anticonvulsant drugs to include a warning in their labelling and to develop a Medication Guide to be provided to patients prescribed these drugs to inform them of the risks of suicidal thought or actions.

In addition, the PhVWP has agreed upon a class wording for anti-epileptics concerning suicidal thoughts and behaviour in December 2008.

RMS' comment: The current SPC includes the wording for anti-epileptics concerning suicidal thoughts and behaviour. No action is necessary. Currently, an article 30 Referral to harmonise the product information of Topamax is pending. The MAH should commit to revise the SPC in line with the text agreed upon in the addressed referral procedure.

Changes to the Reference Safety Information

The Company Core Data Sheet (CCDS) from April 2006 serves as the reference safety information (RSI). The MAH states that there were no changes of the CCDS in the period under review.

RMS' comment: After inclusion of the PhVWP text concerning suicidal thought and behaviour the SPC is considered adequate.

Adverse events

The MAH identified 13 case reports from literature: nine serious unlisted cases and four serious listed case reports. It concerns case reports for which the product under review could not be ruled out.

In these serious unlisted case reports the following (unlisted) adverse events terms were reported: drug interaction (n=5), toxic acute liver disease (n=4), angle closure glaucoma acute (n=1), pneumonia (n=1), glucose blood increased (n=1), serum potassium decrease (n=1), bicarbonate decreased serum (n=1), tremor (n=1), myoclonus (n=1), pseudotumor cerebri (n=1), hyperchloremic acidosis (n=1), anorgasmia (n=1) and renal tubular acidosis (n=1). The serious listed cases all concern the occurrence of acute angle closure glaucoma.

Drug interactions

Drug interaction was the most frequently reported adverse event. It concerns the following drug interactions: The MAH identified one case report including four cases of a drug interaction in which topiramate, valproic acid and acetaminophen was involved leading to acute hepatic injury. It concerns four children in the age of 15 months (2 times), 19 months and 3 years with Dravet syndrome (severe myoclonic epilepsy). In one child there was a positive dechallenge after discontinuation of acetaminophen and in the other cases there was a positive dechallenge after discontinuation of topiramate. The authors suggested that the accumulation of metabolites of acetaminophen due to inhibition of cytochrome P450 enzymes by valproic acid and topiramate could be responsible for hepatotoxicity. The MAH comments that increase in liver function tests, hepatitis and hepatic failure are listed as well as the drug interaction with valproic acid. However, the drug interaction with acetaminophen is unlisted. The MAH further comments that the safety and effectiveness of topiramate is not established under the age of two years. The MAH will continue to monitor possible drug interactions, in particular between valproic acid and topiramate.

RMS' comment: There were four cases of acute hepatic injury in relation to the drug interaction between topiramate and acetaminophen with a positive dechallenge. Although off-label prescribing for age was involved, the MAH should closely monitor this drug interaction taking into account the severity of the adverse event that occurred.

Closely monitoring of the drug interaction between valproic acid and topiramate is accepted and new case reports involving such interaction should be discussed in next PSUR.

Furthermore, there was one case of myoclonus in association with the treatment with topiramate and fluvoxamine. There was a positive dechallenge after topiramate discontinuation. The MAH comments that this interaction is unlisted, but that tremors are a listed adverse reaction of topiramate. It concerns an isolated event according to the MAH. The MAH will continue to monitor possible drug interactions.

RMS' comment: There was only one case reported. However, the case reported a positive dechallenge. Therefore, the MAH should closely monitor the drug interaction between topiramate and fluvoxamine and discuss such new case reports in next PSUR.

Fatal cases

There were no fatal cases reported in the period under review.

Other cases

The MAH also presented 16 case reports from literature in which the product under review was not involved, because the cases were reported in countries in which the product under review is not on the market. The MAH presented the individual case history of each case and assessed each case as listed or unlisted.

There was one case reported of severe hyperthermia, rhabdomyolysis and shock during the treatment of topiramate and olanzapine. The MAH comments that rhabdomyolysis is unlisted, but that hyperthermia is listed. High ambient temperature and oligohydrosis might have contributed to hyperthermia in this patients and the addition of olanzapine with topiramate may have further impaired the patients's ability to sweat.

RMS' comment: It is highly appreciated that in this PSUR the MAH also presented 16 case reports from literature in which the product under review was not involved, because the cases were reported in countries in which the product under review is not on the market.
Concerning the case report of rhabdomyolysis in relation to the interaction with olanzapine: It concerns an isolated case. No further action is required at the moment.

Furthermore, there was one case report of two siblings with neonatal hypocalcemia seizures and transient hypoparathyroidism after topiramate pregnancy exposure. These cases are addressed and discussed under the heading "Pregnancy and lactation".

The remaining cases reported contained the following unlisted adverse events: heatstroke (n=3), reversible facial myoclonus cerebellar (n=2), hyperthyroidism (n=1), cognitive affective disorder (n=1), non-fluent aphasia and frontal hypoperfusion (n=1), cerebrospinal fluid acidosis associated with hyperventilation, dementia while on topiramate treatment for depression (off-label indication) (n=1), neuroleptic malignant syndrome (n=1), hypomania (n=1), potomania (n=1), delusional parasitosis (n=1) and panic attacks (n=1).

RMS' comment: Regarding heatstroke: Heatstroke is unlisted, but hyperthermia is listed. No further action is required at the moment.
Regarding facial myoclonus cerebellar: Facial myoclonus cerebellar, but 'unvoluntary movement disorders' is listed. No further action is required at the moment.
The other cases concern isolated cases or might be due to the underlying disease or concomitant medication. No action is deemed necessary at the moment.

Studies

Newly analysed studies
 None.

Targeted new safety studies
 None.

Published safety studies

The MAH identified the following two safety studies from literature.

In the study of Knudsen et al. the concomitant use of topiramate and valproic acid was studied in association with hypothermia. Twenty-two case reports of hypothermia during topiramate use were identified in the US AERS database and explored. The outcome was that the pharmacodynamic interaction between topiramate and valproic acid may cause hypothermia.

The MAH commented that hypothermia is unlisted for topiramate as well as for valproic acid. Comorbidity (e.g. hyperammonemia and hypothyroidism) was considered to be a confounding factor in the observed association. The MAH commits to monitor possible drug interactions, especially between topiramate and valproic acid.

RMS' comment: Closely monitoring of the interaction between topiramate and valproic acid is accepted. The MAH should address and discuss this interaction in the next PSUR, in specific in association with the occurrence of hypothermia, unless it will be considered necessary within the EU PSUR harmonisation project (DLP January 2009, Sweden=pRMS) that hypothermia needs to be included in the SPC.

Sun et al. conducted a study on changes in cognitive processes in epilepsy in patients treated with topiramate or valproic acid. Thirty patients were included in the study. The authors concluded that there was minor cognitive impairment in these patients as reflected in reaction speed, visual perception, attention adjustment and full-scale intelligence quotient and that topiramate could cause deterioration of all these functions.

The MAH comments that cognitive problems and difficulties in attention are listed, although a decrease in the intelligence quotient is not. The disease itself may have contributed to the further decrease in attention and cognitive functions according to the MAH. No action was considered necessary.

RMS' comment: The rationale of the MAH is accepted. No further action is required.

Lack of efficacy

There was no new efficacy related information.

Risk Management Plan

None.

Post authorisation safety commitment

None.

Drug interactions,

There were four cases reported of a drug interaction in which topiramate, valproic acid and acetaminophen was involved leading to acute hepatic injury. Furthermore there was one case reported of an interaction with fluvoxamine and one case of an interaction with olanzapine. These cases are addressed and discussed under the heading “adverse events”.

Overdose

No new safety information was received regarding overdose or its treatment.

Drug abuse or misuse of product and medication errors

No new safety information regarding this topic was received.

Special patient groups

Children

There were four cases of a drug interaction in which topiramate, valproic acid and acetaminophen were involved leading to acute hepatic injury. All cases concern (very) young children. There was also one case report of a 14-year-old girl with bipolar disorder who developed severe hyperthermia, rhabdomyolysis and shock in association with the concomitant use of topiramate and olanzapine. These cases are addressed and discussed under the heading “Adverse events”.

There were two siblings with neonatal hypocalcemic seizures in relation to topiramate exposure during pregnancy. These cases are addressed in discussed under the heading “Pregnancy and lactation”.

Elderly

There was one case report of a 77-year-old female patient who developed dementia in relation to topiramate and one literature study on hypothermia in association with the concomitant use of topiramate and valproic acid (age of patients ranged from 3.5 to 82 years). No new safety issues were identified.

Organ impaired patient

No new and significant safety information on experience in organ impaired individuals became available to the MAH in the reviewed period.

Pregnancy and lactation

One pregnant patient was reported who presented decreased vision and electronegative electroretinogram while on topiramate in the second trimester. This patient is also addressed under the heading “Long-term treatment”.

In addition, there is one case report of two siblings with neonatal hypocalcemia seizures and transient hypoparathyroidism after topiramate pregnancy exposure. The authors of the case report concluded that topiramate exposure *in utero* in both patients could have resulted in low parathyroid hormone levels; thus decreasing their skeletal calcium reserves, which in turn could have impaired the infants’ ability to respond to the physiologic stress on the calcium-parathyroid hormone axis in the neonatal period and thus could have also contributed to the observed hypocalcemia.

The MAH comments that hypocalcemic seizures in neonates due to topiramate pregnancy exposure are unlisted. However, the MAH indicates that topiramate should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

The MAH received 31 case reports from the UK Epilepsy and Pregnancy Register concerning the major and minor congenital malformations in topiramate pregnancy-exposed infants. These cases are included in the

prospective observational study of Hunt et al. There were 203 pregnancies resulting in 16 neonates with a major congenital malformation (9.0%). Three cases were observed in monotherapy exposures and 13 in topiramate exposure as part of a polytherapy regime. There were four cases of oral clefts (2.2%) and four cases of hypospadias (5.1%). The authors concluded that the number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. Overall, the rate of oral clefts observed was 11 times the background rate. Although the present data provide new information, they should be interpreted with caution due to the sample size and wide confidence intervals.

The MAH comments that topiramate should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus. The occurrence of hypospadias in male infants exposed to topiramate *in utero* is listed, but the occurrence of congenital malformation like cleft lip and bilateral cleft palate, sacral dimple, congenital abnormalities of hip joint, toe webbing, pyloric stenosis, hernia, hydrocele, hydronephrosis, tracheo-esophageal fistula, anal atresia, as seen in the infants included in the study of Hunt et al, are not. The occurrence of congenital abnormalities especially patent ductus arteriosus with topiramate either as monotherapy or in combination with other anti-epileptics is a significant finding and hence will be monitored by the MAH in future.

RMS' comment: Closely monitoring of congenital abnormalities especially patent ductus arteriosus with topiramate either as monotherapy or in combination with other anti-epileptics is accepted. The MAH should also closely monitor the risk on oral cleft after pregnancy exposure to the combined treatment of valproic acid and topiramate. Current data are not convincing to require an SPC update on this topic at this moment.

Patient/consumer reports

The MAH did not receive any medically unconfirmed reports during the period under review.

Effects of long-term treatment

The MAH presented the following three cases:

One patient developed renal tubular acidosis after 10 year of treatment with topiramate. One patient developed vitelliform lesions in the macula and electronegative electroretinogram in her second trimester of pregnancy after topiramate treatment (4 years).

Another patient developed neuroleptic malignant syndrome while receiving topiramate with other psychotropic treatment and after cessation of smoking. The patient had an extended treatment with high doses of neuroleptics in his medical history.

The MAH comments that the review of these cases does not suggest significant alteration in the safety profile of topiramate after long-term treatment.

RMS' comment: It all concerns isolated cases. No action is required at the moment.

Late-breaking information

The MAH received two serious unlisted case reports and one serious listed case report after DLP of the current PSUR. The unlisted case reports concern one case of staghorn calculus and one case of auditory and visual hallucination. The MAH comments that staghorn calculus is a form of renal calculus, which is a listed adverse reaction. Hallucination, not specified, is also listed. The MAH will include these case reports in the next PSUR.

RMS' comment: No new safety issues were identified. Including the reported cases in the next PSUR is accepted.

1.3 Clinical Expert Statement

The MAH states that all cases of adverse drug reactions have been reviewed against all experience to date. The MAH considers that the number of case reports confirms the beneficial safety profile of topiramate, taking into account the large patient exposure. The MAH concludes that the available evidence suggests that the benefit/risk ratio for topiramate remains unaltered.

RMS' comment: The safety information presented in the Clinical Expert Statement is the same as presented in the submitted PSUR. The RMS considers that there is a positive risk/benefit profile of the product under review. Therefore, Renewal of the Marketing Authorisation can be granted provided that the issues raised in the conclusions are resolved.

I.4 PSUR

In view of the EU worksharing project, the next allocated DLP of PSURs of topiramate containing product is January 2012. The MAH should submit the next PSUR, covering the period January 2009 – January 2012, within 60 days after DLP.

I.5 Product information

No changes to the product information are proposed.

RMS' comment: Currently an article 30 referral to harmonise the product information of the innovator product Topamax is pending. The MAH should commit to update the product information accordingly as soon as possible after approval of the referral.

I.6 Manufacturing authorisations / GMP declarations

GMP active substance

The MAH has provided a statement on GMP for the active substance manufacturer signed by the qualified person from the manufacturer responsible for batch release.

Manufacturing licenses

For this renewal the RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

I.7 Conclusions

Renewal of the Marketing Authorisations can be granted with unlimited validity, provided that the following issues are resolved:

- The MAH should commit to update the product information accordingly as soon as possible after approval of the referral.
- The MAH should closely monitor the following safety issues and discuss these issues in next PSUR:
 - Drug interaction with acetaminophen (including details of new case reports)
 - Drug interaction with valproic acid, among others in relation to the occurrence of hypothermia (including details of new case reports). Of note, it may be necessary within the EU PSUR harmonisation project (DLP January 2009, Sweden=pRMS) that hypothermia needs to be included in the SPC.
 - Drug interaction with fluvoxamine (including details of new case reports)
 - Congenital abnormalities such as oral clefts and patent ductus arteriosus with topiramate either as monotherapy or in combination with other anti-epileptics (e.g. valproic acid).

In view of the EU worksharing project, the next allocated DLP of PSURs of topiramate containing product is January 2012. The MAH will submit the next PSUR, covering the period January 2009 – January 2012, within 60 days after DLP.

The renewal procedure ended positively on **29 June 2009**.

The common renewal date is set on **30 September 2009**.