CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Topiramaat CF 25 mg, 50 mg,100 mg, 200 mg, film-coated tablets Centrafarm Services 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/947/001- 004/DC
Registration number in the Netherlands: RVG 34569-34572

Date of first publication: 20 October 2009
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Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX11
Route of administration:	oral
Therapeutic indication:	adjunctive therapy for epileptic patients with partial onset seizures and/or generalised tonic clonic seizures; monotherapy of epileptic patients with partial onset seizures and/or generalised tonic clonic seizures; second line treatment for migraine prophylaxis.
Prescription status:	prescription only
Date of authorisation in NL:	30 January 2008
Concerned Member States:	Decentralised procedure with DK, NO (withdrawn on 15-7-2010), SE
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 CF 25 mg, 50 mg,100 mg, 200 mg, film-coated tablets, from Centrafarm Services B.V.. The date of authorisation was on 30 January 2008 in the Netherlands.

The product is indicated for:

- adjunctive therapy for epileptic patients with partial onset seizures and/or generalised tonic clonic seizures in adults and adolescents aged 12 years and older.
- monotherapy of epileptic patients with partial onset seizures and/or generalised tonic clonic seizures in adults and adolescents aged 12 years and older.
- second line treatment for migraine prophylaxis in adults (not intended for acute treatment).

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

Topiramate is a novel 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 decentralised procedure concerns a generic application claiming essential similarity with the innovator products Topamax, film-coated tablets 25 mg, 50 mg, 100 mg and 200 mg respectivelywhich have been registered in the United Kingdom by Janssen-Cilag since 1995. In the Netherlands, Topamax 25/50/100/200 mg film-coated tablets have been registered since 1999 (NL Licence RVG 24165-24168). 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 Germany. 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. These generic products can be used instead of their 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.

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 these product types 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
The active substance is topiramate, an established active substance which is not described in the European or British Pharmacopoeia (Ph.Eur., BP*). 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. 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/EMEA 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 characterised.

Quality control of drug substance
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. Batch analytical data have been provided for 2 production batches. Both batches complied with the proposed specification.

Stability of drug substance
Stability data have been obtained during storage at 2-8°C, 25°C/60% RH and 40°C/75% RH. The drug substance was packaged in the commercial packaging. The substance is unstable at 40°C. The stability was continued for six months at 25°C/ 60% RH and then stopped. The long term storage conditions have therefore been changed to 2-8°C. At 25°C/ 60% RH the studies were continued for 6 months and then stopped. Based on the stability data provided, at 25°C/ 60% RH from the stability carried out for 6 months, a re-test period of 9 months at 25°C has been fixed. 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
Topiramaat CF 25 mg contains as active substance 25 mg of topiramate, and is a white, circular, biconvex film-coated tablet with a cross-scored breaking notch.
Topiramaat CF 50 mg contains as active substance 50 mg of topiramate, and is a light yellow, circular, biconvex film-coated tablet.
Topiramaat CF 100 mg contains as active substance 100 mg of topiramate, and is yellow, circular, biconvex film-coated tablets.
Topiramaat CF 200 mg contains as active substance 200 mg of topiramate, and is a dark pink, circular, biconvex film-coated tablet.

The film-coated tablets are packed in Al/Al blister packs containing 60 film-coated tablets.

The excipients are:
Tablet Core
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised maize starch
Crospovidone
Silica, colloidal anhydrous
Magnesium stearate

Film-coat 25 mg
Opadry White containing:
Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 400
Talc

Film-coat 50 mg and 100 mg
Opadry Yellow containing:
Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 400
Talc
Iron oxide yellow

Film-coat 200 mg
Opadry Pink containing:
Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 400
Talc
Iron oxide red

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients used are common in the manufacture of tablets and some are also present in the innovator product. The formulation of the 25 / 50 / 100 / 200 mg tablet strengths is linearly proportional. The packaging materials are usual and suitable for the product at issue.

Manufacturing process
The tablets are prepared from a common mixture. The tabletting mixture is compressed and subsequently coated. Each tablet strength has a different colour. The manufacturing process has sufficiently been described. Process validation results for pilot scale (at least 10% of production scale) batches of the 25,

50, 100 and 200 mg tablets have been provided. Process validation for three production scale batches of each strength will be performed post authorisation.

Quality control of drug product
The product specification for the tablets includes tests for appearance, identification, uniformity of dosage units, average mass, disintegration, dissolution rate, related substances, assay and microbiological requirements. The proposed tests and requirements are acceptable. Batch analysis data have been provided on three pilot batches of each strength, demonstrating compliance with the release requirements.

Stability tests on the finished product
Stability data on the product have been provided for three pilot-scale batches of each strength in accordance with applicable European guidelines. The tablets were stored at 25°C/60% RH, 30°C/65%RH and 40°C/75% RH. The product is shown to be stable at long term and intermediate conditions. A decrease in assay is seen at accelerated conditions. However, no significant trend or out of specification is seen. The claimed shelf-life of 30 months and no storage conditions with regard to temperature could be granted. The product should be stored in the original package for protection against humidity. Based on stability data presented post approval, the granted shelf-life was extended to 36 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only material of animal origin. Lactose is produced from milk of healthy animals in the same conditions as milk collected for human consumption and prepared without the use of other ruminant materials than calf rennent. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

These products are generic formulations of Topamax 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets, which are 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 a bioequivalence study in which the pharmacokinetic profile of the test product Topiramaat CF 200 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Topamax 200 mg film-coated tablets from the German market.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results in different member states (DK, NL, NO and SE).

Topiramate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of topiramate. Therefore, a food interaction study is not deemed

necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Bioequivalence study
A single-dose, 2-way cross-over bioequivalence study was carried out under fasted conditions in 24 healthy subjects (19 male/5 female), aged 19-44 years. Each subject received a single dose (200 mg) of one of the 2 topiramate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 10 days. Blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, and 96 hours after administration of the products.
Seven subjects were smokers (less than 5 cigarettes or equivalent per day). All 24 subjects completed the study entirely and were eligible for pharmacokinetic analysis.
The analytical method was adequately validated and a validation report was provided. The applied statistical methods were found approvable.

Results

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

Treatment N=24	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg /ml	**t_{max}** h	**$t_{1/2}$** h
Test	129.7 ± 26.3	142.6 ± 28.8	4.51 ± 0.91	1.25 (0.50 – 5.0)	28 ± 5
Reference	128.5 ± 25.5	141.8 ± 27.1	4.50 ± 0.85	2.50 (0.50 – 6.0)	29 ± 7
***Ratio (90% CI)**	1.01 (0.98-1.04)	1.00 (0.97-1.04)	1.00 (0.95-1.05)	---	---
CV (%)	5.5%	6.3%	10.0%	---	---

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 CF 200 mg tablets and the German reference Topamax 200 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
C_{max} values were observed in the first sampling point (0.5 h after administration) in 9 subjects after administration of the Test formulation, and in 6 subjects after administration of the Reference formulation. Regarding the observation of C_{max} values at the first sampling point (0.5 h after administration) a first sampling point at 0.25 h would have been more adequate. However considering the fact that the obtained 90% confidence interval for C_{max} is rather small, a different outcome is not expected.

Extrapolation of results
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. The results of the bioequivalence study performed with the 200 mg strength therefore apply 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
There has been more than 10 years experience with topiramate containing medicinal products and these have been marketed in many EU countries for many years. The safety profile of topiramate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

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. One pilot test (n=3) and three test rounds (per round n=10) were performed with 33 participants in total (for the 3rd and 4th round aged 20-80). Participants were recruited who suffered from the indication, had relatives or close friends suffering from the indication or could imagine that they would suffer from the indication. In total there were 21 questions (5 open questions, 2 introduction questions and 14 finding/comprehensibility/applicability). This is considered acceptable. The test result provided in the test report was > 90% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Topiramaat CF 25 mg, 50 mg,100 mg and 200 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Topamax, film-coated tablets 25 mg, 50 mg, 100 mg and 200 mg. 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, package leaflet and labelling are in the agreed templates and are in agreement with other topiramate containing products.

The Board followed the advice of the assessors.

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 CF 25 mg, 50 mg, 100 mg and 200 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 30 October 2007. Topiramaat CF 25 mg, 50 mg, 100 mg and 200 mg film-coated tablets were authorised in the Netherlands on 30 January 2008.

The MAH will submit PSURs in accordance with the Data Lock Point of the innovator product Topamax (31 January 2009). This means that the first PSUR will cover the period from October 2007 to January 2009, after which the PSUR submission cycle will be 3 years.

The date for the first renewal will be: 30 September 2012.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to perfom process validation for three production scale batches of each strength.

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 and PIL to suicidal warning for anti-epileptics	NL/H/947/ 001-004 /II/001	II	16-10-2008	3-11-2008	Approval	Y
Replacement or addition of a site where batch control/testing takes place	NL/H/947/ 001-004 /IA/002	IA	17-8-2009	31-8-2009	Approval	N
Extension of shelf-life from 30 to 36 months (finished product).	NL/H/947/ 001-004 /IB/003	IB	24-8-2009	23-9-2009	Approval	N
Adaption of SmPC and PL according to the outcome of Art. 30 referral procedure of the originator product Topamax.	NL/H/947/ 001-004 /IB/004	IB	29-12-2009	28-1-2010	Approval	N
Withdrawal of the marketing authorisaion on Norway.	NL/H/947/ 001-004/ MR	Withdrawal	---	15-7-2010	---	N
• Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate. • Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. Extension or introduction of a re-test period/storage period supported by real time data. • Changes in the manufacturing process of the active substance. • Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance. Tightening of specification limits. • Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance. Addition of a new specification parameter to the specification with its corresponding test method. • Changes in the manufacturing process of the active substance. • Changes in the manufacturing process of the active substance. Change in batch size (including batch size ranges) of active substance or intermediate. Up to 10-fold increase compared to the currently approved batch size.	NL/H/947/ 001-004 /IB/005/G	IB/G	21-10-2010	20-11-2010	Approval	N
• Minor changes in test procedure for the finished product. • Change in test procedure for	NL/H/947/ 001-004 /IA/006/G	IA/G	21-10-2010	20-11-2010	Approval	N

the finished product. Minor change to an approved test procedure. • Change in test procedure for the finished product. Minor change to an approved test procedure.						

Annex I – Type II variation, amendments of SPC and PIL for anti-epileptics

Final SPC and PIL wording agreed by PhVWP July 2008

Summary of Product Characteristics

Section 4.4 Special Warnings and Precautions for Use
Suicidal behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for <*drug substance*>. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge."

Package Leaflet

Section 2 Before you take X
Take special care with
A small number of people being treated with anti-epileptics such as <<drug substance>> have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor."