PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Symtopiram 25/50/100/200 mg film-coated tablets
SymPhar Sp. z.o.o., Poland

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/1233/01-04/MR
Registration number in the Netherlands: RVG 100250-3

25 August 2009

Pharmacotherapeutic group: other antiepileptic agents
ATC code: N03AX11
Route of administration: oral
Therapeutic indication: Adults and adolescents aged 12 years and older: Adjutant therapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures; monotherapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.
Adults: second-line therapy for migraine prophylaxis.

Prescription status: prescription only
Date of first authorisation in NL: 24 July 2007
Withdrawal in NL: 16 April 2009
Concerned Member States: Mutual recognition procedure with PL
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.
INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Symtopiram 25/50/100/200 mg film-coated tablets, from SymPhar Sp. z.o.o. The date of authorisation was on 24 July 2007 in the Netherlands.

The product is indicated in:

- **Adults and adolescents aged 12 years and older** as adjuvant therapy for epileptic patients with partial onset seizures and/or generalised tonic clonic seizures and as monotherapy for epileptic patients with partial onset seizures and/or generalised tonic clonic seizures.

- **Adults** as second-line therapy for migraine prophylaxis.

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 the Topamax authorisation in Poland (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 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/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 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 ≥ 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 at page 11, variation NL/H/1233/001-004/IA/003.

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 Symtopiram 200 mg film-coated tablets (SymPhar Sp. z.o.o., Poland) 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 ± SD, t\textsubscript{max} (median, range)) of topiramate under fasted conditions.

<table>
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<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t} µg.h/ml</th>
<th>AUC\textsubscript{0-∞} µg.h/ml</th>
<th>C\textsubscript{max} µg/ml</th>
<th>t\textsubscript{max} h</th>
<th>t\textsubscript{1/2} h</th>
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<tr>
<td>Test</td>
<td>155.4 ± 28.0</td>
<td>160.3 ± 29.0</td>
<td>4.2 ± 0.9</td>
<td>1.33(0.25-4)</td>
<td>49.6 ± 18.8</td>
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<tr>
<td>Reference</td>
<td>154.0 ± 25.8</td>
<td>158.5 ± 25.7</td>
<td>4.3 ± 0.9</td>
<td>1.33(0.5-5)</td>
<td>47.2 ± 17.7</td>
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<td>*Ratio (90% CI)</td>
<td>1.01 (0.98-1.03)</td>
<td>1.01 (0.98-1.03)</td>
<td>0.97 (0.90-1.03)</td>
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<td>CV (%)</td>
<td>3.2</td>
<td>4.5</td>
<td>11.0</td>
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AUC\textsubscript{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\textsubscript{0-∞} area under the plasma concentration-time curve from time zero to infinity
C\textsubscript{max} maximum plasma concentration
t\textsubscript{max} time for maximum concentration
t\textsubscript{1/2} half-life

*In-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\textsubscript{0-t}, AUC\textsubscript{0-∞} and C\textsubscript{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 Symtopiram 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 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

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 Symtopiram 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 subheader: The subheader 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

Symtopiram 25/50/100/200 mg film-coated tablets have a proven chemical-pharmaceutical quality as 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. Symtopiram was authorised in the Netherlands on 24 July 2007.

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 Symtopiram 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\text{\textsubscript{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\textsubscript{\frac{1}{2}} Half-life
\text{t_{max}} Time for maximum concentration
TSE   Transmissible Spongiform Encephalopathy
USP   Pharmacopoeia in the United States
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