Public Assessment Report

Scientific discussion

Topiramaat Aurobindo 25 mg, 50 mg, 100 mg and 200 mg, film-coated tablets

(topiramate)

NL/H/2916/001-004/MR

Date: 26 May 2014

This module reflects the scientific discussion for the approval of Topiramaat Aurobindo. The procedure was finalised on 26 February 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Topiramaat Aurobindo 25 mg, 50 mg, 100 mg and 200 mg, film-coated tablets from Aurobindo Pharma B.V.

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 SmPC.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Topamax film-coated tablets, which was first registered by Janssen-Cilag Ltd in the UK in July 1995. In the Netherlands, Topamax 25 mg, 50 mg,100 mg and 200 mg tablets (NL License RVG 24165-24168) have been registered by Janssen Cilag B.V. since 30 June 1999.

The concerned member states (CMS) involved in this procedure were Cyprus, France, Italy, Malta, Romania, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Topiramaat Aurobindo 25 mg are white, circular, biconvex, film-coated tablets debossed 'E' on one side and '22' on the other side.
Topiramaat Aurobindo 50 mg are light yellow coloured, circular, biconvex, film-coated tablets debossed 'E' on one side and '33' on the other side.
Topiramaat Aurobindo 100 mg are dark yellow coloured, circular, biconvex with bevelled edge, film-coated tablets debossed 'E' on one side and '23' on the other side.
Topiramaat Aurobindo 200 mg are pink coloured, circular, biconvex with bevelled edge, film-coated tablets debossed 'E' on one side and '24' on the other side.

The film-coated tablets are packed in polyamide/aluminium/PVC blister packs and HDPE bottles with polypropylene closure containing silica gel sachets as desiccant.

The excipients are:
Tablet core: microcrystalline cellulose (E460), lactose monohydrate, pregelatinized maize starch, sodium starch glycolate (type A) and magnesium stearate (E572).
Tablet coating: hypromellose (E464), titanium dioxide (E171), macrogol 400, polysorbate 80, iron oxide yellow (E172) (only 50/100 mg) and red iron oxide (E172) (only 200 mg).

The 25 mg, 50 mg and 100 mg strengths are dose proportional. The 200 mg tablet is not dose-proportional to the lower tablet strengths.

II.2 Drug Substance

The active substance is topiramate, an established active substance which is not described in the European Pharmacopoeia (Ph.Eur.), but is described in the Pharmcopoeia of the United States (USP). The active substance is a white to off-white powder and is freely soluble in methylene chloride. Topiramate is a chiral molecule but shows no polymorphism.

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.

Manufacturing process
A one stage synthesis process is used. No class 1 solvents are used in the synthesis, nor are metal catalysts. Acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH and is in line with the USP, with additional requirements for residual solvents, microbial contamination, particle size and bulk density. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (3 months). Out of specifications occurred at accelerated conditions (description), hence testing at intermediate conditions was commenced. The proposed retest period of 24 months, when stored below 30°C, is justified. No additional data is required.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies included the optimisation of the granulation process. Bioequivalence studies have been performed with 100 mg and 200 mg product. The formulation of these tablets was the same as the proposed formulation. The quantitative and qualitative compositions of the Dutch and UK reference products are identical. A biowaiver has been proposed for the 25 mg and 50 mg strength and can be granted on quality grounds The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a wet granulation process, in which either a common blend is made (for 25 mg, 50 mg and 100 mg) or a separate blend is made (for 200 mg). The blend is then compressed into tablets, which are film-coated and packaged.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled/smallest production scale and three maximum production scaled batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for intermediate production scaled batches will be performed post authorization.

Control of excipients
The excipients comply with Ph.Eur. requirements or in-house requirements (coating agents). The individual components of the coating agents comply with either Ph.Eur. requirements or National Formulary requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units (mass variation), assay, related substances, microbial contamination, identification of colouring agents (titanium dioxide and iron oxide) and thickness. The release and shelf-life limits are identical, except for thickness which is not included in the shelf-life specification. The specifications are acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on two pilot scaled/smallest production scale and three maximum production scaled batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two smallest production scale batches of each strength stored at 25°C/60% RH (6 months) and 30°C/75% RH (6 months). Previously results of stability studies of up to 24 months at 25°C/60% and 12 months at 30°C/75% were provided of two batches of each strength. The conditions used in the stability studies are not fully according to the ICH stability guideline, as the 30°C/75% RH storage condition has a higher relative humidity than mentioned in the guideline. This condition is however acceptable. The batches were stored in Alu-Alu blisters or multi-dose white opaque HDPE bottles with white opaque polypropylene closuring having an induction sealing wad and containing silica gel sachets as desiccant.
At accelerated conditions out of specifications were observed at 6 months for description, and at long-term conditions the description went out of specification for description at 36 months. Photostability has been demonstrated for the drug product. The proposed shelf-life of 24 months when stored below 25°C is justified.

Stability data has been provided demonstrating that the product remains stable for 6 months in-use shelf-life following first opening of the container, when stored at 25°C/60% RH. An in-use period is not considered necessary as no changes occurred.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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. Lactose monohydrate is produced from milk fit for human consumption and calf rennet that complies with EU requirements. Magnesium stearate is produced from stearic acid derived vegetable origin of palm oil.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Topiramaat Aurobindo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
The following post-approval commitment was made:

- The MAH committed to continue the ongoing stability studies of the submission batches and to carry out long-term stability studies on a minimum of one marketed production batch per year.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Topiramaat Aurobindo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Topamax tablets, which is available on the European market. Reference is made tot the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Topiramate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Topiramaat Aurobindo 100 mg and 200 mg, film-coated tablets (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Topamax 100 mg and 200 mg tablets (Janssen-Cilag Limited, 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. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The RMS considers that the analytical method has been adequately validated and is acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Biowaiver
A biowaiver has been justified for the 25 mg and 50 mg, based on the criteria below:

- Topiramaat Aurobindo 25 mg, 50 mg & 100 mg tablets are manufactured by the same manufacturer and using the same manufacturing process.
- The pharmacokinetics of topiramate is linear over the therapeutic dose range.
- The qualitative composition of Topiramaat Aurobindo 25 mg, 50 mg and 100 mg tablets is the same.
- Topiramate 25 mg & 50 mg tablets are dose proportional (i.e. step-down formula) with Topiramate 100 mg tablets, *i.e*. the ratio of amount of active substance and the excipients are the same for all the strengths.
- The dissolution profile of Topiramate 25 mg & 50 mg tablets is similar to the Topiramate 100 mg tablet, in different media: 0.1M HCl, pH 4.5 acetate buffer, water & pH 6.8 phosphate buffer.

Bioequivalence study I - 100 mg tablets
Design
An open label, randomized, two treatment, two sequence, two period, crossover, single-dose comparative oral bioequivalence study was carried out under fasted conditions in 36 healthy Indian male subjects, aged 18-35 years. Each subject received a single dose (100 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. There was a washout period of 30 days between the two periods of the study.

Blood samples were collected before dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, 144.0, 192.0 and 240.0 hours post dose.

Results
32 subjects completed the study successfully. Two subjects dropped out from the study on period II, as they did not report to the study centre on the check-in day. One subject tested positive for a breath alcohol test and one person got an adverse reaction, both were withdrawn from the study.
In total 30 subjects were included in pharmacokinetic and statistical analysis, since two other subjects were withdrawn from bioanalysis as they did not fulfil at least three half-lifes of sampling.

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

Treatment N=30	AUC_{0-t} µg.h/ml	$AUC_{0-\infty}$ µg.h/ml	C_{max} µg/ml	t_{max} h	$t_{1/2}$ h
Test	127.7 ± 31.6	136.6 ± 33.2	3.0 ± 0.7	2.00 (0.25 – 4.00)	60.32 ± 15.47
Reference	131.9 ± 28.2	138.8 ± 30.9	3.0 ± 0.7	2.25 (0.5 – 5.00)	58.74 ± 13.65
***Ratio (90% CI)**	0.97 (0.93 – 1.02)	0.99 (0.95 – 1.03)	0.99 (0.94 – 1.05)	-	-
CV (%)	11.27	9.65	12.15	-	-

$AUC_{0-\infty}$ 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*

Bioequivalence study II – 200 mg tablets

Design

An open label, randomized, two treatment, two sequence, two period, crossover, single-dose comparative oral bioequivalence study was carried out under fasted conditions in 36 healthy Indian male subjects, aged 19-32 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. There was a washout period of 30 days between the two periods of the study.

Blood samples were collected before dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, 144.0, 192.0 and 240.0 hours post dose.

Results

30 subjects completed the study successfully. One person withdrew his consent before cannulation and one subject was withdrawn from the study after 0.75 hour post dose in period I due to an adverse event. In period II three subjects dropped out, as they did not report to the study centre on the check-in day. One subject was withdrawn after 24 hour post dose due to an adverse event. In total 29 subjects were analysed, since one subject was withdrawn from bioanalysis as he did not fulfil at least three half-lifes of sampling.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of topiramate under fasted conditions.

Treatment N=29	AUC_{0-t} µg.h/ml	$AUC_{0-\infty}$ µg.h/ml	C_{max} µg/ml	t_{max} h	$t_{1/2}$ h
Test	242.4 ± 49.9	250.03 ± 49.1	6.618 ± 0.9	1.50 (0.50 – 4.00)	51.42 ± 15.9
Reference	245.4 ± 54.9	251.4 ± 56.4	6.662 ± 1.2	2.00 (0.50 – 4.00)	45.86 ± 14.5
***Ratio (90% CI)**	0.99 (0.96 – 1.02)	1.00 (0.98 – 1.02)	1.00 (0.96 – 1.04)	-	-
CV (%)	5.75	5.39	9.01	-	-

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence studies

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 Aurobindo 100 and 200 mg are bioequivalent to and Topamax 100 and 200 mg tablets with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 MEB has been assured that the bioequivalence studies have 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Topiramaat Aurobindo film-coated tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	Nephrolithiasis Acute myopia and secondary angle closure glaucoma Metabolic acidosis Mood changes and depression Suicide/suicide ideation Major congenital malformations with use in pregnancy Hypothermia with concomitant valproic acid Oligohydrosis Hyperammonaemia with or without encephalopathy with or without concomitant valproic acid
Important potential risks	–
Important missing information	–

The MAH included the safety concerns in line with the reference product Topamax. Routine risk minimisation activities and routine pharmacovigilance are considered sufficient. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Topamax. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product.
The member states consider the RMP adequate. In conclusion, this generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

No user testing was performed. Instead, a bridging report was submitted, referring to the successfully user tested package leaflet (PL) of another Topiramaat Aurobindo 25 mg, 50 mg, 100 mg and 200 mg, film-coated tablets product (Parent PL). The bridging statement justifies the waiver for readability testing, since the text is the same in both PLs. Both leaflets have the same layout and design (the same in-house style), same font type and same text colour. The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Topiramaat Aurobindo 25 mg, 50 mg, 100 mg and 200 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Topamax 25 mg, 50 mg, 100 mg and 200 mg 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 Board followed the advice of the assessors. The marketing authorization for Topiramaat Aurobindo was granted in the Netherlands on 30 November 2010.

The concerned member states, on the basis of the data submitted, mutually recognized the Dutch assessment for marketing authorization. Essential similarity has been demonstrated for Topiramaat Aurobindo 25 mg, 50 mg, 100 mg and 200 mg, film-coated tablets with the reference product. There was no discussion in the CMD(h). The mutual recognition procedure was finalised with a positive outcome on 26 February 2014.

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