CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Topiramaat Mylan 25, 50, 100 and 200 mg, film-coated tablets Mylan 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/717/01-04/DC
Registration number in the Netherlands: RVG 33418-33421
27 April 2009

Pharmacotherapeutic group:	antiepileptics, other
ATC code:	N03AX11
Route of administration:	oral
Therapeutic indication:	adults and adolescents aged 12 years and older: 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. adults: second line treatment for migraine prophylaxis (not intended for acute treatment).
Prescription status:	prescription only
Date of authorisation in NL:	14 August 2007
Concerned Member States:	25, 50 and 100 mg: decentralised procedure with AT, BE, CZ, DE, DK, EL, FI, IT, NO, PL, SE, SI, SK and UK 200 mg: decentralised procedure with AT, BE, DE, DK, EL, FI, IT, NO, PL, SE, SI 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 concerned member states have granted a marketing authorisation for Topiramaat Mylan 25, 50, 100 and 200 mg, film-coated tablets, from Mylan B.V., the Netherlands. The date of authorisation was on 14 August 2007 in the Netherlands.

The product is indicated in:

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

- Adults as second line treatment for migraine prophylaxis (not intended for acute treatment).

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

Topiramate is a 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 product Topamax 25, 50, 100 and 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 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 two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Topamax 25 and 200 mg, film-coated tablets registered in the United Kingdom. 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 products.

No new preclinical 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.

II.1.1 Active substance and excipients

The active substance is topiramate, an established active substance described in the draft monograph of the USP. USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the United States. Topimarate is a white or almost white powder. No polymorphic forms of topiramate are known.

Manufacture
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.

The manufacturing process is adequately explained. Acceptable specifications are laid down for starting materials and reagents.

Specification
The active substance specification is considered adequate to control the quality and meets the requirements of the draft monograph in the USP. The other in-house requirements are acceptable. The methods have been sufficiently described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 24 months. Based on the data submitted, a retest period could be granted of 24 months years when stored in the original package in order to protect from humidity and light.

II.1.2 Medicinal Product

Composition
Topiramaat Mylan 25 mg film-coated tablets contain as active substance 25 mg topiramate and are white, round, biconvex, film-coated tablets debossed with "G" on one side and "TO" over "25" on the other.
Topiramaat Mylan 50 mg film-coated tablets contain as active substance 50 mg topiramate and are yellow, round, biconvex, film-coated tablets debossed with "G" on one side and "TO" over "50" on the other.
Topiramaat Mylan 100 mg film-coated tablets contain as active substance 100 mg topiramate and are yellow, round, biconvex, film-coated tablets debossed with "G" on one side and "TO" over "100" on the other.
Topiramaat Mylan 200 mg film-coated tablets contain as active substance 200 mg topiramate and are red, round, biconvex, film-coated tablets debossed with "G" on one side and "TO" over "200" on the other.

The tablets are packed in Aluminium-Aluminium foil blisters.

The excipients are:
Tablet core: microcrystalline cellulose, povidone K29-32, silica (colloidal anhydrous), sodium, starch glycolate (type A), magnesium stearate.

Film-coat:
Topiramaat Mylan 25: Opadry White YS-1-7003 (titanium dioxide E171, hypromellose E464, macrogol 400, polysorbate 80)
Topiramaat Mylan 25: Opadry Yellow 03B92164 (titanium dioxide E171, hypromellose E464, macrogol 400, iron oxide yellow E172)
Topiramaat Mylan 25: Opadry Yellow 03B19280 (titanium dioxide E171, hypromellose E464, macrogol 400, iron oxide yellow E172).
Topiramaat Mylan 25: Opadry Maroon 05B16131 (titanium dioxide E171, hypromellose E464, macrogol 400, Allura Red Aluminium Lake E129, Sunset Yellow Aluminium Lake E110, Indigo Carmine Aluminium Lake E132).

The used excipients are well known and safe in the proposed concentrations. All excipients are of Ph.Eur. quality, except for the Opadry filmcoatings, which conform to in-house requirements. The colourants used in the coating solution have E-numbers and are authorised for use in foods.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging materials are usual and suitable for the product at issue. The MAH has committed to provide the results of tests for compliance of the packaging material with Ph.Eur. requirements when available.

The objective was to develop a product that would be essentially similar to the innovator product Topamax.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for one pilot batch (10% of the intended maximum batch size) of each strength in accordance with the relevant European guidelines. The process only involves standard steps and the content of active substance in the tablet is high. Validation data on production scale are therefore not required prior to registration. Process validation for full-scale batches will be performed post authorisation.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on Ph.Eur. monographs (i.e. GP.012 and GP.057) and in-house specifications, and includes tests for identification of drug substance and colourants, dissolution, assay, related substances, sulphate/sulphamate, microbiological purity, water content, and uniformity of dosage units. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product, though the shelf-life limits for water content are wider than at release and will be re-evaluated (post-approval) when stability data of the whole shelf-life are available..

Satisfactory validation data for the analytical methods have been provided, where relevant.

Batch analysis data on 3 pilot scaled batches of topiramate tablets of all four strengths have been provided, demonstrating compliance with the specification. For the 25, 100 and 200 mg tablets, one of the three batches is made at the development site. The other batches have been produced at the proposed production site.

Stability tests on the finished product
Stability data on the product have been provided for at least two batches of each strength in both bulk packaging and the proposed packaging (Al/Al blister) in accordance with applicable European guidelines demonstrating the stability of the final product at long term conditions over 18 months*:* On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are*: "Store in the*

original package in order to protect from light and moisture." The MAH has committed to place the first three production-scale batches on stability trial and to providing the stability data, at the end-of-the-authorised shelf-life of the products.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

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 two bioequivalence studies in which the pharmacokinetic profile of the test product Topiramaat Mylan 25 mg is compared with the pharmacokinetic profile of the reference product Topamax 25 mg and in which the pharmacokinetic profile of the test product Topiramaat Mylan 200 mg is compared with the pharmacokinetic profile of the reference product Topamax 200 mg.

The choice of the reference products in the bioequivalence studies have been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Topiramate can 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 studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioequivalence study 1
A single-dose, randomised, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy non-smoking subjects, aged 20-52 years. Each subject received a single dose (25 mg) of one of topiramate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There was a 21-day washout interval between the 2 dose administrations. Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after administration.
Four subjects were withdrawn from the study, one was dismissed for non-compliance and three subjects withdrew for personal reasons. Twenty subjects were therefore eligible for pharmacokinetic analysis (10 males and 10 females).

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

Treatment N=20	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13.23 ± 3.90	16.08 ± 4.15	0.28± 0.01	1.13 (0.67-6)	70.8 ± 12.3
Reference	13.07 ± 3.80	15.92 ± 3.94	0.29 ± 0.15	0.67 (0.33-4)	71.3 ± 13.2
***Ratio(90% CI)**	101.1 (96.7-105.5)	100.6 (96.2-105.0)	98.4 (92.8-104.3)	-	-
CV (%)	7.97	7.75	10.65	-	-

$AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ extrapolation was found to be more than 20% in nearly 50% of the cases. When data from subjects with $AUC_{0-\infty}$ extrapolation of more than 20% were excluded, the 90%CI for $AUC_{0-\infty}$ Test/Reference range was 97.2-107.8. As the last time point for blood sampling was 168 h, the absorption phase has been completely covered. According to the Note for Guidance CPMP/EWP/QWP/1401/98, AUC0-t is the principle outcome for bioequivalence studies. Moreover, bioequivalence was also demonstrated when these subject were excluded from statistical analyses. Therefore the outcomes of this study can be considered as bioequivalent.

Bioequivalence study 2

A single-dose, randomised, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy non-smoking subjects, aged 19-54 years. Each subject received a single dose (200 mg) of one of topiramate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There was a 21-day washout interval between the 2 dose administrations. Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after administration.
Four subjects were withdrawn from the study, one was dismissed due to emesis within 4 hours of dosing of the test product and three subjects withdrew for personal reasons. Twenty subjects were eligible for pharmacokinetic analysis (12 males and 8 females).

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

Treatment N=20	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	141.1 ± 20.9	145.5 ± 20.9	4.8 ± 0.9	1.5 (0.33-3)	36.9 ± 5.8
Reference	140.0 ± 23.3	144.6 ± 23.6	4.6 ± 4.7	1.0 (0.33-6)	38.3± 5.9
***Ratio(90% CI)**	101.1 (98.7 - 103.5)	100.9 (98.6 -103.3)	103.2 (97.2 - 109.5)	-	-
CV (%)	4.3	4.3	10.9	-	-

$AUC_{0-\infty}$ 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*

AUC0-inf and t½ could be calculated for all subjects, for both the Test and Reference product. AUCextrapolated varied between 1.37-6.58%.

Conclusion bioequivalence studies

In both the 25 mg and 200 mg the 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 the test tablets (Topiramaat Mylan 25 and 200 mg) and reference tablets (Topamax 25 and 200 mg) are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

In both studies, the incidence of study discontinuation is relatively high (4 out of 24), though equally divided over Test and Reference product. The sample size of 24 was based on intra-subject CV of approximately 20 and 30% for AUC and C_{max}, respectively. However, according to the current Note for Guidance, the number of subjects is more than sufficient. Therefore, the number of 20 subjects pro study is accepted.

The 25 and 200 mg tablets are dose proportional with the 50 and 100 mg tablets. The pharmacokinetics of the active substance are linear in the range 10-400 mg. The results of the bioequivalence study performed with the 25 and 200 mg therefore apply to the other strengths with intermediate dosages.

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).

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
During the decentralised procedure a discussion was held regarding the use of topiramate in children less than 12 years of age. In the SPC of the Dutch innovator Topamax the use of topiramate in children less than 12 years of age is not explicitly mentioned in the indication. Further in section 4.4 it is stated that there is limited experience on the use of topiramate in children aged 12 years and under.
Initially, the proposed SPC for Topiramaat Mylan 25/50/100/200 mg by the applicant, gave a clear dose recommendation with respect to the use of topiramate in children less than 12 years of age. There were no age restrictions. Furthermore, the indication was extended to Lennox-Gastaut syndrome (LGS).
However, the data in the separate clinical expert rapport supporting the above are insufficient. Of note in adults with epilepsy, topiramate is not the first choice, given its safety profile. The benefit/risk of topiramate used in children may be different compared to adults. Therefore, the use of topiramate in children below 12 years of age has not been approved.
Furthermore, reference is made to the MR-procedure with Topiramate Sandoz (FI/H/599/01-04), in which most member states were involved. For those products, the use in children below 12 years of age and the indication Lennox-Gastaut syndrome were also not approved.

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Topamax marketed by Janssen-Cilag.

Readability test
The applicant has provided a report on readability for a lamotrigine containing product and asks for a waiver for conducting readability on the current PIL. A diagnostic readability test (technical readability/traceability/comprehensibility/applicability) including scoring has been performed on the English version of the PIL. Testing was performed with in total 22 participants of whom 2 were included in a pilot test and 10 in each of the subsequent two rounds of user testing. The results of the pilot test have not been reported which is deemed acceptable.
Following the first round, including 10 participants, the text has been adapted taking into account the results of the test. The second test with the adapted text, performed with another 10 participants, showed that the text was sufficiently improved and no further amendments were made. There were sufficient questions about the critical sections. The questions covered the following areas sufficiently: technical readability, traceability, comprehensibility and applicability. The conclusions are sufficiently clear, concise and clearly presented. The patient information leaflet has been adapted sufficiently taking into account the results of the test.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Topiramaat Mylan 25, 50, 100 and 200 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Topamax 25, 50, 100 and 200 mg, 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 reference product. 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 Mylan 25, 50, 100 and 200 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 11 February 2007. Topiramaat Mylan 25, 50, 100 and 200 mg, film-coated tablets are authorised in the Netherlands on August 14th 2007.

A European harmonised birth date has been allocated (18 January 2006) and subsequently the first data lock point for topiramate is January 2009. The first PSUR will cover the period from February 2007 to January 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 11 February 2012.

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

Quality - medicinal product

- The MAH has committed to provide the results of tests for compliance of the packaging material with Ph.Eur. requirements when available.
- The MAH has committed to place the first three production-scale batches on stability trial and to providing the stability data, at the end-of-the-authorised shelf-life of the products.

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
Change in the name of the medicinal product.	NL/H/0717/ 001-004/IB/ 001	IB	22-4-2008	6-6-2008	Approval	N
Change in the name and/or address of the marketing authorisation holder.	NL/H/0717/ 001-004/IA/ 002	IA	23-4-2008	7-5-2008	Approval	N
Adaptation of SPC section 4.4 and PIL section 2 to suicidal warning for anti-epileptics	NL/H/0717/ 001-004/II/ 003	II	5-11-2008	14-1-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder. This change only affects the MAH Mylan in Belgium.	NL/H/0717/ 001-004/IA/ 004	IA	22-1-2009	5-2-2009	Approval	N