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M E B

PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Oxcarbazepine Mylan 150, 300, and 600 mg film-coated tablets
Mylan B.V., the Netherlands

oxcarbazepine

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/716/001-003/DC
Registration number in the Netherlands: RVG 33444, 33445, 33446

29 July 2009

Pharmacotherapeutic group:	antiepileptics, carboxamide derivatives
ATC code:	N03AF02
Route of administration:	oral
Therapeutic indication:	treatment of partial seizures with or without secondarily generalised tonic-clonic seizures, and as monotherapy or adjunctive therapy in adults and children of 6 years of age and above
Prescription status:	prescription only
Date of authorisation in NL:	25 January 2007
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, EL, ES, FI, FR, 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 member states have granted a marketing authorisation for Oxcarbazepine Mylan 150, 300, and 600 mg film-coated tablets, from Mylan B.V. The date of authorisation was on 25 January 2007 in the Netherlands. The product is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures, and for use as monotherapy or adjunctive therapy in adults and in children of 6 years of age and above.

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

The pharmacological activity of oxcarbazepine is primarily exerted through the active metabolite 10-mono-hydroxy-carbamazepine (MHD). The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to anticonvulsant effects. No significant interactions with brain neurotransmitter or modulator receptor sites were found.
Oxcarbazepine and its active metabolite (MHD), are potent and efficacious anticonvulsants in animals. They protected rodents against generalised tonic-clonic and, to a lesser degree, clonic seizures, and abolished or reduced the frequency of chronically recurring partial seizures in Rhesus monkeys with aluminium implants. No tolerance (i.e. attenuation of anticonvulsive activity) against tonic-clonic seizures was observed when mice and rats were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Trileptal, which has been registered in Denmark by Novartis since 8 June 1990 (original product). In the Netherlands, Trileptal (NL RVG 24750, 24751 and 24752) has been registered since 2000 by the procedure DK/H/168/001-004. In addition, reference is made to Trileptal authorisations in the individual member states (reference product). The innovator product Trileptal is not authorised in Slovenia and reference is made to a so called 'EU-generic'. Therefore, in agreement with Denmark who was the RMS for the innovator product Trileptal the relevant assessment reports for the innovator have been supplied.

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 Trileptal, 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. 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.

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
The active substance Oxcarbazepine is not described in the Ph. Eur. or in other leading compendia. The drug substance is an off-white to yellow crystalline powder and is sparingly soluble in chloroform. Oxcarbazepine produced by the active substance manufacturer is of polymorphic form A. Oxcarbazepine does not exhibit stereochemistry or other types of isomerism. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.

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 and 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 use in the medicinal product.

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 for 12 months. No specific storage conditions are needed.

<u>Manufacture</u>
The material is purchased and then micronised to the MAH’s specifications. The micronised material was compared to the untreated oxcarbazepine in studies aimed at determining the crystal form: Thermal analysis, X-ray diffraction, IR spectrophotometry, microscopic inspection. No differences were seen; the micronisation process does not change the crystal form. The particle size limits are set so as to assure consistent bioavailability, similar to the reference product.

<u>Specification</u>
The drug substance specification is generally in line with the Pharmacopeial Forum. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.

<u>Stability</u>
The MAH refers to the ASMF. Since he did not change the packaging and since no special storage temperature is required, this is acceptable. A retest period could be granted of 12 months without specific storage conditions.

** 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
Oxcarbazepine Mylan 150, 300, and 600 mg film-coated tablets contain as active substance 150, 300 and 600 mg mg of oxcarbazepine respectively. They are oblong, buff-coloured, and convex, and coated with and inner (white) and an outer (buff) coating. They have a break line and the embossment "OX | 150 mg (or "OX | 300 mg or "OX | 600mg) on one side, and "G | G" on the other side. The dimensions of the elliptical faces are 11.0 by 5.5 mm (150 mg), 15.0 by 6.5 mm (300 mg), and 18.5 x 8.0 mm (600 mg). The break line is there to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in clear PVC-PVdC / aluminium blisters, or in polypropylene tablet containers with polyethylene caps and optional polyethylene ullage filler, depending on pack size.

The excipients are:

Tablet Core: Crospovidone, Hypromellose E3, Cellulose – microcrystalline, Silica - colloidal anhydrous and Magnesium stearate.

Tablet coating: Black iron oxide (E172), Hypromellose, Lactose Monohydrate, Macrogol 4000, Red iron, oxide (E172), and Titanium Dioxide (E171).

The contents of the three tablet formulations, 150, 300 and 600 mg, are dose proportional. The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs except for the iron oxides in the buff Opadry coating mixture (the outer coating of the tablets). For this excipient the specifications and test results are sufficiently presented in the dossier.

Pharmaceutical development
The 600 mg tablets were developed to be bioequivalent to the innovator tablets; the lower strengths were then developed to be proportional. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients used are normal for the product type. The chemical-pharmaceutical information on the test and reference batches of the bioequivalence study is acceptable. The packaging materials are usual and suitable for the product at issue.

Manufacturing process and quality control of the medicinal product
The manufacturing process is based on wet granulation, tablet compression, and spray coating. It is a standard process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product has been presented for 9 batches in accordance with the relevant European guidelines. The MAH has committed to provide full-scale validation data post approval.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The product specifications cover appropriate parameters for this dosage form, and include tests for appearance, uniformity of mass, thickness, hardness, average weight, friability, identification, disintegration, dissolution rate, dose uniformity, assay, microbiological purity, related substances and identification of colour. Validation study results of the analytical methods are presented. The batch analysis results of 9 batches demonstrate that the finished products meet the proposed specifications.

Breakability
The tablets have break lines similar to the innovator tablets. The half tablets comply with the Ph. Eur. tests for Uniformity of Mass of Single Dose Preparations. A full test report was agreed on.

Stability tests on the finished product
Stability data on the product have been provided from nine 150 mg batches, seven 300 mg batches and seven 600 mg batches in accordance with applicable European guidelines. The stability control tests and their acceptance limits are adequate to determine the stability. The proposed shelf-life of 24 months with storage below 30°C for the drug product can be approved. The labelled storage conditions are; "store below 30ºC". The MAH committed that the first three production scale batches will be placed on a stability programme as per the marketed stability protocol.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is certified to be free of TSE risks. For magnesium stearate a certificate of suitability issued by the EDQM has been provided. 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

Pharmacodynamic, pharmacokinetic and toxicological properties of oxcabazepine are well known. As oxcarbazepine is a widely used, well-known active substance, no further studies are required for this application and the applicant provides none. Overview based on literature review is, thus, appropriate.

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 oxcarbazepine 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

Oxcarbazepine 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 Oxcarbazepine Mylan 600 mg is compared with the pharmacokinetic profile of the reference product Trileptal 600 mg, from the UK market.

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

A single-dose, 4-way replicate cross-over bioequivalence study was carried out under fasted conditions in 60 healthy subjects (44 males, 16 females), aged 19-55 years. The 4-way replicated design was applicated to address the high intra subject variability in the pharmacokinetic variable C_{max}. The design is considered acceptable, especially because scaling may be possible with this design. The applied statistical method is acceptable.
Each subject received a single dose (600 mg) of one of the 2 oxcarbazepine formulations. The tablets were orally administered in solid form with 240 ml water after an overnight fast of at least 10 h. Fasting was continued for 4 hrs after dosing. There were 2 dosing periods, separated by a washout period. of 7 days. The sequence was either test-reference-test-reference or reference-test-reference-test

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 16, 24, 36, and 48 hours after administration of the products.

Fourty-nine out of 60 volunteers were non smokers, and 11 subjects smoked 10 or less than 10 cigarettes a day. Three subjects withdrew from the study prior to Period II due to personal reasons and two volunteers were withdrawn from the study prior to period II due to adverse events and did not show up for confinement. One subject was withdrawn prior Period III as the volunteer did not show up for confinement, and two subjects withdrew prior Period IV due to personal reasons. Fifty-two subjects completed the study and were eligible for pharmacokinetic analysis. Plasma samples were analysed for oxcarbazepine and its active metabolite MDH (Tables 1 and 2). 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_{max} (median, range)) of oxcarbazepine under fasted conditions.

Treatment N=52-	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test 1st admin*	6398 ± 1438	6626 ± 1449	1584 ± 804	1.64 ± 1.08	11.3 ± 1.9
Test 2nd admin	6921 ± 1639	7136 ± 1667	1839 ± 737	1.69 ± 1.17	11.4 ± 1.9
Reference 1st admin	6654 ± 1582	6881 ± 1585	1783 ± 939	1.39 ± 0.84	11.4 ± 1.8
Reference 2nd admin	6767 ± 1621	6988 ± 1659	1718 ± 745	1.58 ± 1.06	11.6 ± 1.9
***Ratio (90% CI)**	0.99 (0.96-1.02)	0.99 (0.97-1.01)	0.96 (0.87-1.05)	---	---
CV Test (%)	10.4	9.6	42.9	---	---
CV Reference (%)	9.9	9.7	36.1	---	---

$AUC_{0-\infty}$ 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
† administration (the study design is a duplicate design)

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 10-mono-hydroxy-carbamazepine (MDH) under fasted conditions.

Treatment N=52	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test 1st admin†	200604 ± 28090	230923 ± 37151	8082 ± 2321	6.49 ± 4.45	14.7 ± 5.9
Test 2nd admin	204225 ± 31343	231854 ± 40400	8570 ± 1674	5.69 ± 2.77	13.7 ± 2.7
Reference 1st admin	204335 ± 31319	233979 ± 37399	8133 ± 1665	6.10 ± 2.69	14.1 ± 3.2
Reference 2nd admin	207678 ± 31584	233827 ± 39838	8491 ± 1399	5.76 ± 2.78	13.6 ± 2.2
***Ratio (90% CI)**	0.98 (0.96-1.00)	0.99 (0.97-1.01)	0.99 (0.95-1.02)	---	---
CV Test (%)	6.5	7.4	16.5	---	---
CV Reference (%)	6.6	8.0	10.3	---	---

$AUC_{0-\infty}$	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
†	administration (the study design is a duplicate design)

**ln-transformed values*

Oxcarbazepine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of oxcarbazepine. 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.

Parent drug: Based on the pharmacokinetic parameters of the parent drug oxcarbazepine, the reference and test tablet are considered bioequivalent with respect to the extent and rate of absorption. For oxcarbazepine, the ratio of AUC_{0-t}/AUC_{inf} were all well above 80%. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of oxcarbazepine are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The data indicate that regarding C_{max} a high intra-subject variability is observed.
Metabolite: Also based on the pharmacokinetic parameters of the active metabolite 10-mono-hydroxy-carbamazepine under fasted conditions, it can be concluded that test and the reference tablet are bioequivalent with respect to rate and extent of absorption. For MDH the ratio of AUC_{0-t}/AUC_{inf} after the first administration of test, in 3 cases, and after the second administration, in 5 cases, the ratio of AUC_{0-t}/AUC_{inf} were below 80%. For the reference this was 6, respectively 1 case. No high intra-subject variability is observed for the pharmacokinetic variables AUC0-t, $AUC_{0-\infty}$ and C_{max}.

The MAH considered the metabolite the main analyte for proof of bioequivalence. However, the parent drug is also active, and can be accurately measured in this study. Even more, the use of the pharmacokinetics of the parent drug is more sensitive to detect differences in the rate of absorption (C_{max}). In addition, the pharmacokinetics of the parent and the active metabolite shows linear pharmacokinetics.[1] The parent drug is considered the analyte for proof of bioequivalence by the MEB. This does not change the conclusion of this study, as bioequivalence was proven for both parent and metabolite.

Based on the submitted bioequivalence study Oxcarbazepine Mylan 600 mg is considered bioequivalent with Trileptal 600 mg tablets. The 600 mg tablets are dose-proportional with the 150 mg and the 300 mg mg tablets. The tablets have been manufactured by the same manufacturing process and oxcarbazepine shows linear pharmacokinetics.

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
Oxcarbazepin was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of oxcarbazepine 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.

[1] May et al, Clinical pharmacokinetics of oxcarbazepine. Clin. Pharmacokinet. (2003) 42 (12):1023-42

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Trileptal marketed by Novartis.

Readability test
The MAH has provided a report on readability for a lamotrigine containing product and asked for a waiver for conducting readability on the current PIL, since the products belong to the same therapeutic class and the product information is very similar on key-issues.

Readability report on Lamotrigine Tablets
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 20 participants, 10 in each of the subsequent two rounds of user testing. 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.

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

Oxcarbazepine Mylan 150, 300 and 600 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Trileptan 150, 300 and 600 mg, respectively. Trileptan 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 oxcarbazepine 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Oxcarbazepine Mylan 150, 300 and 600 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 22 December 2006. Oxcarbazepine Mylan 150, 300 and 600 mg tablets were authorised in the Netherlands on 25 January 2007.

The PSUR submission cyclus is 3 years. The first PSUR will cover the period from December 2006 to december 2009.

The date for the first renewal will be: December 2011.

The following post-approval commitments were made during the procedure:

Quality
- Full validation will be conducted on the first three commercial scale batches of each strength.
- In-Process Granule testing to be performed on first ten production batches only.
- Microbial Purity testing to be performed on the first three succeeding production batches and thereafter to test one in every 10 batches or at least one batch annually.
- Identification of Opadry Colour test to be tested on a minimum of one batch annually.
- The MAH committed that the first three production scale batches will be placed on a stability programme as per the marketed stability protocol.

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
MHD	10-mono-hydroxy-carbamazepine
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
Replacement or addition of a manufacturing site or part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms.	NL/H/0716/001 -003/IA/001	IA	10-9-2007	24-9-2007	Approved	N
Change in the name of the medicinal product to reflect the purchase of Merck Generics by Mylan Inc.	NL/H/0716/001 -003/IA/002	IB	16-6-2008	16-7-2008	Approved	N
Change in the name and/or adress of the marketing authorization holder.	NL/H/0716/001 -003/IA/003	IA	16-6-2008	30-6-2008	Approved	N
Deletion of the registered assembler, QC and batch releaser in Spain.	NL/H/0716/001 -003/IA/004	IA	21-7-2008	4-8-2008	Approved	N
Change in the name of the batch releaser and packager in France.	NL/H/0716/001 -003/IA/005	IA	8-9-2008	11-11-2008	Approved	N
Change in the pack size of the product. New pack size of 60 tablets is registered.	NL/H/0716/001 -003/IA/007	IA	27-10-2008	10-11-2008	Approved	N
Type II safety warnings on suicidal thoughts in antiepileptics; adaptation of section 4.4 of the SPC and section 2 of the PIL to the PhVWP recommendations.	NL/H/0716/001 -003/IA/008	II	20-10-2008	23-10-2008	Approved	Y, Annex I
Change in the name and/or address of the marketing authorization holder.	NL/H/0716/001 -003/IA/009	IA	25-2-2009	11-3-2009	Approved	N
Change in the name of the medicinal product. The Marketing Authorisation holder wishes to amend the medicinal product name in ES only in order to meet commercial requirements.	NL/H/0716/001 -003/IB/010	IB	16-3-2009	15-4-2009	Approved	N

Annex I to the PAR

Type II variation – Antiepileptics and suicidal behaviour

This variation was made for the inclusion of safety warnings insection 4.4 of the SPC and section 2 of the PIL according to the PhVWP recommendations (agreed on by July 2008).

Summary of Product Characteristics

"Section 4.4 Special Warnings and Precautions for Use
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 oxcarbazepine

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 oxcarbazepine have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor."