Public Assessment Report

Scientific discussion

Oxcarbazepine Jubilant 150 mg, 300 mg and 600 mg, film-coated tablets (oxcarbazepine)

NL/H/2793/001-003/DC

Date: 11 June 2014

This module reflects the scientific discussion for the approval of Oxcarbazepine Jubilant. The procedure was finalised on 2 December 2013. 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 Oxcarbazepine Jubilant 150 mg, 300 mg and 600 mg, film-coated tablets from Jubilant Pharmaceuticals N.V.

The product is indicated for partial seizures with or without secondarily generalised tonic-clonic seizures as monotherapy or adjunctive therapy in adults and children aged 6 years and above.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Trileptal 150 mg, 300 mg and 600 mg film-coated tablets (NL License RVG 24750-24752) which have been registered in the Netherlands by Novartis Pharma B.V. since 8 February 2000 through MRP DK/H/0168/001-003 (original product).

The concerned member states (CMS) involved in this procedure were Denmark, Malta and the United Kingdom (all strengths), and additionally for the 300 mg and 600 mg strengths the member states Cyprus, Latvia, Lithuania and Estonia were involved.

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

II. QUALITY ASPECTS

II.1 Introduction

Oxcarbazepine Jubilant 150 mg is a pale grey green colored, oval shaped, biconvex film-coated tablet, scored on both sides and debossed with '150' on one side of the score line on one side of the tablet.
Oxcarbazepine Jubilant 300 mg is a yellow colored, oval shaped, biconvex film-coated tablet, scored on both sides and debossed with '300' on one side of the score line on one side of the tablet.
Oxcarbazepine Jubilant 600 mg is a pink colored, oval shaped, biconvex film-coated tablet, scored on both sides and debossed with '600' on one side of the score line on one side of the tablet.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in PVC/PE/PVDC blisters with aluminium foil backing.

The excipients are:
Tablet core - silica (dental type) (E551), microcrystalline cellulose (E460), hypromellose (E464), crospovidone (Ph. Eur. type A) (E1202), magnesium stearate (E470b)
Tablet coating - hypromellose (E464), titanium dioxide (E171), macrogol 8000, Iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172) (only in 150 mg tablets), talc (E553b)

The different strengths are dose proportional.

II.2 Drug Substance

The active substance is oxcarbazepine, a well-known active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or faintly orange crystalline powder, which is practically insoluble in water. Oxcarbazepine exhibits polymorphism. Form A is manufactured.

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 reaction scheme, a flow chart and a brief description of the manufacturing process were provided. The manufacturing process and in-process controls are sufficiently described. Each of the manufacturing steps has been validated for three consecutive full-scale batches.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph, with additional specification. The specification is acceptable in view of the route of synthesis and the various European guidelines. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three consecutive full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for one pilot-scale and six full-scale batches stored at 25°C/60% RH (max. 60 months) and 40°C/75% RH (6 months). The batches were stored in the same immediate packaging as the commercial packaging. The data demonstrate the stability of the drug substance and supports a retest period of 4 years when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical development
The aim of the development was to produce a product that is stable, pharmaceutically equivalent as well as bioequivalent to the originator product, Trileptal tablets. The development of the product has been described, the choice of excipients is justified and their functions explained. Dissolution and impurity profiles for all three strengths of drug product were found to be similar to those for the reference products. The dissolution profile of the strength used in the bioequivalence study (oxcarbazepine 600 mg film-coated tablets) is similar to that of other strengths (*i.e.* 150 mg and 300 mg). Further, the 150 mg and 300 mg strengths have the same qualitative compositions and are quantitatively proportional to the 600 mg strength, and are manufactured by the same manufacturing process. A biowaiver was submitted to extrapolate the results from the bioequivalence study on the 600 mg strength to the 150 mg and 300 mg strengths. The biowaiver criteria are fulfilled.
As indicated in the SmPC, the score line is intended only for ease of swallowing, not for administration of halve dosage forms. Therefore, compliance with the Ph Eur. requirement for subdivision is not deemed necessary.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing of oxcarbazepine film-coated tablets consists of wet granulation, followed by mixing of the granules with the extragranular excipients. Finally, the tablets are film coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale batches per strength.

Control of excipients
All ingredients within the tablet core comply with relevant Ph.Eur monographs. All ingredients of the coating mixture are listed and adequately controlled by pharmacopoeial requirements.

Quality control of drug product
The product specification includes tests for appearance, identity of oxcarbazepine, titanium dioxide and ferric oxide, water, dissolution, assay, related substances, microbial contamination and uniformity of dosage units. The release and shelf-life requirements/limits are identical with the exception of the limits for water and total impurities, which can be accepted.
The analytical methods have been adequately described and validated. Batch analyses data has been provided for two pilot-scale batches per strength, packed in the proposed packaging materials. The results comply with the acceptance criteria.

Stability of drug product
Stability data on the product has been for two pilot-scaled batches per strength stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored packed in the proposed blister packs. Results for photostability testing in accordance with ICH requirements demonstrate that the product is not photosensitive. Based on the provided stability data a shelf-life of 2 years, stored without any special storage conditions, can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is manufactured from fatty acid derived from vegetable sources. Magnesium stearate that is manufactured from fatty acids derived from animal sources may also be used provided the material complies with the recommendations outlined in current version of EMA's "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01)". Representative TSE/BSE certificate from manufacturers of both vegetable source and animal source of magnesium stearate were provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Oxcarbazepine Jubilant has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Oxcarbazepine Jubilant 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 Trileptal film-coated tablets, which is available on the European market. Reference is made to 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

Oxcarbazepine 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Oxcarbazepine Jubilant 600 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Trileptal® 600 mg tablets (Novartis Pharma GmbH, Germany).

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.

Biowaiver

A biowaiver has been granted for the 150 mg and 300 mg strengths, as the conditions listed in section 5.4 of 'Note for guidance on the investigation of bioavailability and bioequivalence' are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturer and process;
- The drug input is linear over the therapeutic dose range;
- The qualitative composition of all the strengths is same;
- The ratio between the amounts of active and excipients is same;
- The dissolution profiles are similar under identical conditions for the additional strengths and the strength used in bioequivalence study.

Bioequivalence study

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, replicate, crossover bioequivalence study was carried out under fasted conditions in 64 healthy male subjects, aged 19-44 years. Each subject received a single dose (600 mg) of one of the 2 oxcarbazepine formulations in four different dosing periods. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 4 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.17, 0.33 0.67, 1.00, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.50, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 48 and 60 hours after administration of the products.

The design of the study is acceptable. The procedures followed for a fasting condition and a wash-out period of 12 days (i.e. at least 5 terminal half-lives to exclude carry-over effects) is agreed. The duration of the sampling is sufficient. The replicate design is acceptable due to high variability of the Cmax and AUC of the test and reference products (*i.e*. CV range: 32-34 % for the test product and 32-37% for the reference product). Food has no effect on the rate and extent of absorption of oxcarbazepine. The use of 600 mg is also agreed as this is the highest strength and in accordance with the bioequivalence guideline.

Analytical/statistical methods

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

Results

Fifty-four (54) subjects completed all the periods of the study. The 10 withdrawals were for the following reasons: 4 subjects due to AEs (3) and protocol non-compliance (1), and 6 subjects dropped out from the study as they failed to show-up for follow up.

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

Treatment N=54	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7755 ± 2656	8296 ± 2710	2480 ± 796	1.0 (0.7 – 3.3)	--
Reference	7683 ± 2442	8167 ± 2522	2515 ± 921	1.4 (0.5 – 4.0)	--
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	1.01 (0.98 – 1.04)	1.00 (0.93 – 1.07)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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 study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Oxcarbazepine Jubilant 600 mg is considered bioequivalent with Trileptal 600 mg tablets.

A total of 5 adverse events (vomiting, headache, dog bite, high ALT) were reported in the study, which were mild to moderate in severity.

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).

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 Oxcarbazepine Jubilant film-coated tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	- hypersensitivity - severe cutaneous reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, - bone marrow depression - hyponatraemia.
Important potential risks	- suicidal ideation and behaviour - teratogenic potential - rhabdomyolysis - interaction with valproate - interaction with SSRI and amphetamine - interactions with anti-coagulants - arthralgia - dysarthria - chest pain - eye disorders after vaccine exposure
Missing information	- pregnancy

For the risks and areas of missing information indicated above, no additional pharmacovigilance activities are considered necessary. Routine pharmacovigilance is considered sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Trileptal. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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. Two stages of testing were performed, each involving 10 subjects, preceded by a preliminary round of testing with 2 subjects. The participants were questioned about the leaflet in an evaluation and problem-seeking test. The questionnaire for this user test contained 17 questions specific to the key safety issues of the product and 4 questions general to the format of the leaflet. The questions sufficiently address the key safety

messages. After the pre-round, as well as after the first round of testing no further amendments were considered necessary.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Oxcarbazepine Jubilant 150 mg, 300 mg and 600 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Trileptal 150 mg, 300 mg and 600 mg film-coated tablets. Trileptal 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.

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 Jubilant 150 mg, 300 mg and 600 mg film-coated with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 December 2013.

There were no post-approval commitments made during the procedure.

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