# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 21-285

## ADMINISTRATIVE DOCUMENTS
## CORRESPONDENCE

K1.1

*K1.1*

N21285

*N21285*

REC.
6/11/01
1:54PM.

# Trileptal ®

(oxcarbazepine)

# Oral Suspension

Novartis

**NDA 21-285**

Action
Package

Volume 1

Anti-Convulsant

## 13. Patent Information

As of the date of this application, there are no patents, as defined in 21 CFR § 314.53(b), relating to the product.

Joseph J. Borovian
Novartis Corporation

APPEARS THIS WAY
ON ORIGINAL

**EXCLUSIVITY SUMMARY for NDA # 21-285 SUPPL # _____**
**Trade Name Trileptal Oral Suspension Generic Name Oxcarbazepine**
**Applicant Name Novartis HFD-120**
**Approval Date 5-25-01**

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_x__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /__x_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__/ NO /_x__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

      YES /___/ NO /__x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__x_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /__x_/

If yes, NDA # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any

drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-014 Trileptal Tablets

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /_x__/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /_/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | |
|---|---|
| Investigation #1 | |
| IND # _____ YES /___/ | NO /___/ Explain: _____ |
| | _____ |
| | _____ |
| Investigation #2 | |
| IND # _____ YES /___/ | NO /___/ Explain: _____ |
| | _____ |
| | _____ |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |
| Investigation #2 | |
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Russell Katz
6/5/01 08:52:12 AM

**PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)**

View as Word Document

| | | | |
|---|---|---|---|
| **NDA Number:** | 021285 | **Trade Name:** | TRILEPTAL(OXCARBAZEPINE) 60MG/ML ORAL |
| **Supplement Number:** | 000 | **Generic Name:** | OXCARBAZEPINE |
| **Supplement Type:** | N | **Dosage Form:** | |
| **Regulatory Action:** | OP | **COMIS Indication:** | MONOTHERAPY/ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN ADULTS WITH EPILEPSY/AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDR |
| **Action Date:** | 7/31/00 | | |

**Indication # 1** monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children 4-16

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: NEW FORMULATION developed with this submission

Comments (if any):

**Ranges for This Indication**

| Lower Range | Upper Range | Status | Date |
|---|---|---|---|
| 1 months | 4 years | Deferred | 5/25/02 |

**This page was last edited on 5/29/01**

(S)

Signature

5/29/01

Date

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ON ORIGINAL

NDA 21-285

Trileptal® (oxcarbazepine) Oral Suspension
New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Michael J. Macalush
Associate Director
Drug Regulatory Affairs

July 26, 2000
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable checkbox.*

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | | |
|---|---|---|
| | See attached spreadsheet | |
| | | |
| | | |

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| Sabri Markabi, MD | Executive Director & Head, Clinical Research & Development NS |
| **FIRM/ORGANIZATION** | |
| Novartis Pharmaceutical Corporation | |
| **SIGNATURE** S. Markabi | **DATE** 29 JULY 2002 |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/CDER/FDA: (301) 443-3454 '99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 2003/03

# DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

The following information concerning See Attached (*Name of clinical investigator*) who participated as a clinical investigator in the submitted study See attached (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

*Please mark the applicable checkbox.*

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| NAME | TITLE |
|---|---|
| Sabri Markabi, MD | a.i. Head, Clinical Research & Development Neuroscience System |
| FIRM/ORGANIZATION: Novartis Pharmaceutical Corporation | |
| SIGNATURE: S. Markabi | DATE: 28/JULY/2000 |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3455 (3/99) Created by Electronic Document Services/USDHHS: (301) [illegible]

# Item 19. Other – Financial Disclosure

## Table of Contents

## Item 19 – Financial Disclosure

**Overview:**

- **Process used to collect information retrospectively**
  - Letters were sent out to all investigators requesting financial disclosure information
  - A follow up letter was sent to investigators if no reply was received after four weeks and an additional letter four weeks later if necessary
  - At study close out and/or as part of retrospective collection the Investigators were told to update Novartis for 1 year from LPLV (last patient last visit) at their site if any change
  - retrospective collection of financial disclosure information (for studies on going 2/2/99)

- **Methods used to minimize bias**
  - independent data monitoring via Novartis or CRO
  - multiple investigators used in the studies
  - double-blind active controlled trials used

- **Desription of Spreadsheets**
  - shows principal investigator, subinvestigators, children & spouses (if applicable)
  - shows forms received
  - shows whether there was something to disclose
  - shows if investigator refused to reply

- **Summary of Findings**
  - There is no financial information to disclose.

APPEARS THIS WAY
ON ORIGINAL

# Number of Pages Redacted 4

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Confidential,
Commercial Information

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: February 13, 2001

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C. T. Viswanathan, Ph.D. GV 2/15/01
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 21-285, Trileptal® (Oxcarbazepine) Oral Suspension, sponsored by Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

TO: Russell Katz, M.D.
Director,
Division of Neuropharmacological Drug Products
(HFD-120)

As requested by HFD-120, the Division of Scientific Investigations initiated an audit of the following bioequivalence study.

**Study CTRI476 0036:** An Open-Label, Randomized, Balanced, Three-way Crossover Study to Compare the Bioavailability of Two Oxcarbazepine Oral Suspension Formulations (F3 and F6) Versus Film-Coated Tablet Formulation (Final Market Image F5) after Single Administration and at Steady State in Healthy Male Subjects.

The clinical site of the study was Medeval Limited, Skelton House, Manchester Science Park, Manchester, England. The plasma samples obtained from the study were shipped to the Bioanalytics Unit, Department of Drug Metabolism and Pharmacokinetics, Novartis Pharma S.A., Ruiel-Malmaison, France, and assayed only for TRI 477, the monohydroxy active metabolite of oxcarbazepine.

Following the inspection, Form FDA-483 was issued at both the clinical (11/9-13/2000) and analytical (11/13-15/2000) sites. Our evaluation of the inspection findings is provided below.

**Medeval Limited, Skelton House, Manchester Science Park, Manchester, England**

1. **Failure to document the times that the oral suspension formulations F3 and F6 were dispensed (using a 10 ml syringe), and that the dose in the syringe was administered within one hour after dispensing as recommended by the sponsor. The dosing information on the label of the syringes (i.e., subject number, treatment number, and dose expiration time) was destroyed and could not be verified.**

   The site agreed to correct the above objectionable observation. They stated that a procedure has been implemented to assure all records related to dosing are kept and maintained.

   During the inspection, we found that a Medeval senior pharmacy technician prepared the study doses. The tablet formulation was put into individual envelopes, and the suspension formulations were transferred to 10-ml syringes shortly before dosing. Although the envelopes, the syringe labels, and the transferred times of the suspension formulations to the syringes were not retained or recorded, the study formulation that each subject received in each dosing period was recorded in the subject case report form, and no discrepancies from the study randomization code were found. The site also has a standard procedure that requires the clinical staff to check the syringe expiration time (i.e., dose in a syringe must be administered within 1 hour of preparation) prior to dosing.

2. **Subject 516 was allowed to enter and complete the study although the ALT levels of this subject were higher than normal at screen and throughout the study.**

   Due to the potential effect of oxcarbazepine to cause elevation of liver enzymes, and as a precaution to protect the rights, safety and welfare of study subjects, Subject 516 should not have been allowed to enter the study. However, as (i) the study is a crossover study, and (ii) that this subject had completed the study, we are of the opinion that the data generated from Subject 516 can be included in the bioequivalence determination.

**Bioanalytics Unit, Department of Drug Metabolism and Pharmacokinetics, Novartis Pharma S.A., Rueil Malmaison, France**

1. **All source stability Data for TRI 477 (monohydroxy active metabolite of oxcarbazepine) are not available on-site. Only a stability report issued in 1991 by Ciba-Geigy Limited, Basle was provided during the inspection.**

   In a written response to the Form FDA-483, Novartis explained that it is their policy to maintain all source data for analytical work at the site where the analysis is performed. Thus, the source stability data for TRI477 are maintained at Basle, Switzerland. To update the TRI477 stability data in a format that is consistent with their current analytical study reports, Novartis submitted an amendment to the 1991 stability report. Following a review of this amendment, we are of the opinion that there is no stability issue with TRI477. TRI477 in spiked QC plasma samples is stable at room temperature for 48 days, and at +4 degrees C for at least 4 months.

**Conclusion:**

We recommend that the data from Study CTRI476 0036 be acceptable for review. After you have reviewed this transmittal memo, please append it to the original NDA submission.

/S/

Martin K. Yau, Ph.D.

**DSI Final Classification:**

**VAI - Medeval Limited, Skelton House, Manchester Science Park, Manchester, England**
**VAI - Bioanalytics Unit, Department of Drug Metabolism and Pharmacokinetics, Novartis Pharma S.A., Rueil Malmaison, France**

cc:

HFA-224
HFD-45 RF
HFD-48 Fujiwara/Yau/CF
HFD-860 Sekar/Baweja
HFD-120 Fanari
HFR-SW350 Kuchenthal
Draft: MKYau 2/13/01
File:5356;O:\BE\EIRCOVER\21285nov.oxc.doc

FACTS # 148486

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: September 29, 2000

TO: Associate Director
International Operations Branch
Division of Emergency and Investigational Operations
(HFC-130)

FROM Stan W. Woollen /S/
Acting Director
Division of Scientific Investigations (HFD-45)

FROM: C.T. Viswanathan, Ph.D. CTV 10/2/00
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2000 **High Priority CDER User Fee NDA**, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

Re: NDA 21-285
DRUG: Trileptal® (Oxcarbazepine) Oral Suspension
SPONSOR: Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

This memo requests you to arrange for an inspection of the clinical and analytical portions of the following bioequivalence study.

Study: Study CTRI476 0036 - An Open-Label, Randomized, Balanced, Three-way Crossover Study to Compare the Bioavailability of Two Oxcarbazepine Oral Suspension Formulations (F3 and F6) Versus Film-Coated Tablet Formulation (Final Market Image F5) after Single Administration and at Steady State in Healthy Male Subjects.

Clinical Site: Medeval Limited
Skelton House
Manchester Science Park
Lloyd Street North
Manchester M15 6SH
England
TEL: 0161-226-6525
FAX: 0161-226-8936

BIMO Assignment, NDA 21-285

Clinical Investigators: Dr. Paul Rolan
Dr. Pawn Narhlya

Sponsor Contact: Ms. Johanne Bonner
TEL: (+44) 1403 323 444
FAX: (+44) 1403 323 290

Please check the batch numbers of both the test and the reference drug formulations used in the study with the descriptions in documents submitted to the Agency. If study formulations have not been submitted to the agency previously, samples of both the test and reference drug formulations should be collected and mailed to the Division of Testing and Applied Analytical Development, St. Louis, MO, for screening.

Please have the records of all study subjects including all signed consent forms audited. The subject records in the NDA submission should be compared with the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, etc., the files of communication between the clinical site and the sponsor should be examined for their contents.

Analytical Site: Bioanalytical Unit
Drug Metabolism & Pharmacokinetics
Novartis Pharma S.A.
Rueil-Malmaison, France
TEL: 011 33 (00331) 47 52 88 84
FAX: 011 33 (00331) 47 52 31 87

Analytical Method: HPLC with UV detection at 210 nm

Contacts: J. Denouel (responsible scientist)
H. Humbert (head of Bioanalytics Unit)

The above assay was used to determine concentrations of oxcarbazepine in subject plasma samples obtained in the study. All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of plasma samples, as well as the variability between and within runs, Q.C., stability, the number of repeat assays of subject plasma samples, and the reasons for such repetitions, if any, should be examined. Acceptance of the specific repeated result should be examined for consistency with the SOP. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

BIMO Assignment, NDA 21-285

Following identification of the investigator, background material including subject records and pertinent data will be forwarded directly. A member of the Bioequivalence Team from the Division of Scientific Investigations will participate in the inspections.

Headquarters Contact Person: Martin K. Yau, Ph.D., (301) 827-5458

BIMO Assignment, NDA 21-285

CC:
HFA-224
HFD-45 RF
HFD-48 Fujiwara/Yau/CF
HFD-120 Fanari
HFD-860 Sekar
DSI:5356; O:\BE\bio21285.doc
Draft: MKY 9/29/2000 MKY 10/2/00

FACTS 148486

FEI Medeval Ltd 10003933318

FEI Novartis Pharma SA 3000274040

/S/ 1/3/00

APPEARS THIS WAY
ON ORIGINAL

**MEMORANDUM**

DATE: May 23, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-285

SUBJECT: Action Memo for NDA 21-285, for the use of Trileptal (oxcarbazepine) Suspension

Trileptal (oxcarbazepine) tablet is a recently approved anticonvulsant. Novartis Pharmaceuticals Corporation, the manufacturer of Trileptal tablets, submitted NDA 21-285 for the use of Trileptal oral suspension on 7/28/00. The application contains CMC information related to the new formulation, as well as the results of a bioequivalence study comparing the performance of the proposed suspension with the marketed tablet.

The application has been reviewed by Dr. Danae Christodoulou, chemist (reviews dated 5/2/01 and 5/23/01), Drs. Vanitha Sekar and Jogarao Gobburu, pharmacokinetics/pharmacometrics reviewers in OCPB, Carol K. Vincent, microbiology reviewer (review dated 5/15/01), Dr. Yeh-Fong Chen, statistician (review of stability data dated 3/30/01), Dr. Jennifer Fan, safety evaluator, OPDRA (review dated 5/4/01), Dr. Ed Fisher, pharmacologist (review dated 5/18/01), and Dr. John Feeney, Neurology Team Leader (memo dated 5/24/01). The review team recommends that the application be approved. I will briefly review the main issues and offer the rationale for the division's action.

As noted in the OCPB review, oxcarbazepine is rapidly reduced to the monohydroxylated derivative (MHD), which is considered the primary active moiety. The bioequivalence study compared 1) the single dose kinetics of the tablet and suspension, and 2) the steady state kinetics of the tablet and suspension.

As Dr. Sekar describes in her review, the AUC of the suspension after a single dose meets equivalence criteria, but not the Cmax (ratio of suspension to tablet 0.77, 90% CI (.72, .82). However, at steady state, equivalence criteria are met for both AUC and Cmax. As she also notes, a single dose study is more sensitive to small differences between products, and is therefore ordinarily relied upon to assess bioequivalence between 2 products. For this reason, the products cannot, technically, be considered to be bioequivalent.

However, the clinical meaning of this "failure" needs to be examined.

As noted in the OCPB review, various attempts have been made to assess the effects of this "failure" on the performance of the suspension relative to the tablet.

Two scenarios have been addressed: initiation of treatment with suspension, and conversion to treatment with suspension once steady state has been achieved with the tablet.

In the first scenario, we can expect steady state to be achieved within 2-3 days, as with the tablet. However, prior to reaching steady state, the Cmax will not be equal to that of the tablet (although, importantly, the AUC will). This slight difference is not expected to have any meaningful clinical impact; within 2-3 days, steady state will be reached, at which point the suspension and tablet perform equally (even with the tablet, during this titration phase full therapeutic effect will not have been obtained; this will also be true for the suspension). For this reason, there is no reasonably expected clinical impact of the slight decrease in Cmax after a single dose (current labeling for the tablet recommends that the dose be increased no more frequently than every 3 days; by that time, steady state would have been expected to have been reached, so, again, the differences in Cmax would have no effect clinically [also see next paragraph]).

Regarding the second scenario, in which a patient at steady state with the tablet is converted to suspension, pharmacokinetic modeling suggests that the decrement in Cmax after the first dose of suspension (compared to what the Cmax would have been if the next dose had been tablet) would be about 7%; this would be expected to be bioequivalent to the Cmax at steady state with the tablet. Subsequent doses of suspension would yield Cmax's even closer to those achieved with the tablet alone. Simulation of the Cmin's yields even smaller differences. Clearly, these differences are not clinically meaningful.

For these reasons, I believe it is eminently reasonable to conclude that the "failure" of the Cmax of the suspension after a single dose is unimportant clinically, and the 2 products can be considered to be functionally equivalent.

There were several other issues raised in several of the reviews.

The microbiology reviewer recommended that the application be approved only upon the firm's commitment to continue microbial limits testing for lot release and periodically throughout the stability protocol. However, Dr. Christodoulou notes in her 5/23/01 review (page 10) that the sponsor has agreed to perform this testing on a lot by lot basis for the first 20 lots, after which they will submit the data to the Agency with an additional proposal for continued testing at this time; she finds this acceptable. For this reason, we will not require the sponsor to make any additional commitment at this time.

Also, Dr. Fan of OPDRA notes that the container label appears to be similar to that of Tegretol (both have a similar blue color), which has the potential to cause

medication errors. For this reason, she recommends that the color on the container label be changed. Further, she recommends that the product be described as being 300 mg/5mL, not 60 mg/mL; the former is more conventional for similar products. We have discussed both of these issues with the sponsor. They have agreed to change the color on the container label to green, and have changed the concentration as requested.

For these reasons, I will issue the attached Approval letter.

Russell Katz, M.D.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Russell Katz
5/25/01 08:06:32 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

# Office of Clinical Pharmacology and Biopharmaceutics
## *New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| NDA Number | 21-285 | Brand Name | Trileptal |
| OCPB Division (I, II, III) | I | Generic Name | Oxcarbazepine |
| Medical Division | Neuropharm | Drug Class | Anti-epileptics |
| OCPB Reviewer | Vanitha J. Sekar | Indication(s) | Partial seizures |
| OCPB Team Leader | Ramana Uppoor | Dosage Form | Oral suspension |
| | | Dosing Regimen | Starting dose: 600 mg/day, as bid dosing Dose may be increased depending on clinical response by a maximum increment of 600 mg/day at approximately weekly intervals, to a maximum dose of 2400 mg/day |
| Date of Submission | 7/31/00, 12/1/000, 12/19/00. 3/16/01 | Route of Administration | Oral |
| Estimated Due Date of OCPB Review | 5/1/01 | Sponsor | Novartis |
| PDUFA Due Date | 5/31/01 | Priority Classification | Standard |
| **Division Due Date** | 5/1/01 | | |

*Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| STUDY TYPE | [redacted] | [redacted] | [redacted] | [redacted] |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | [redacted] | [redacted] | |
| Tabular Listing of All Human Studies | X | [redacted] | [redacted] | |
| HPK Summary | X | [redacted] | [redacted] | |
| Labeling | X | [redacted] | [redacted] | |
| Reference Bioanalytical and Analytical Methods | X | [redacted] | [redacted] | |
| I. Clinical Pharmacology | [redacted] | [redacted] | [redacted] | [redacted] |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | [redacted] | [redacted] | [redacted] | [redacted] |
| ***Healthy Volunteers-*** | | | | |
| **single dose:** | | | | |
| **multiple dose:** | | | | |
| Patients- | [redacted] | [redacted] | [redacted] | [redacted] |
| **single dose:** | | | | |
| **multiple dose:** | | | | |
| Dose proportionality - | [redacted] | [redacted] | [redacted] | [redacted] |
| **fasting / non-fasting single dose:** | | | | |
| **fasting / non-fasting multiple dose:** | | | | |
| Drug-drug interaction studies - | [redacted] | [redacted] | [redacted] | [redacted] |
| **in-vivo effects on primary drug:** | | | | |
| **in-vivo effects of primary drug:** | | | | |
| **in-vitro:** | | | | |
| Subpopulation studies - | [redacted] | [redacted] | [redacted] | [redacted] |
| **ethnicity:** | | | | |
| **gender:** | | | | |
| **pediatrics:** | | | | |
| **geriatrics:** | | | | |
| **renal impairment:** | | | | |
| **hepatic impairment:** | | | | |
| PD: | [redacted] | [redacted] | [redacted] | [redacted] |
| **Phase 2:** | | | | |
| **Phase 3:** | | | | |
| PK/PD: | [redacted] | [redacted] | [redacted] | [redacted] |
| **Phase 1 and/or 2, proof of concept:** | | | | |
| **Phase 3 clinical trial:** | | | | |

| | | | | |
|---|---|---|---|---|
| Population Analyses - | [redacted] | [redacted] | [redacted] | [redacted] |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | [redacted] | [redacted] | [redacted] | [redacted] |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | [redacted] | [redacted] | [redacted] | [redacted] |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | [redacted] | [redacted] | [redacted] | [redacted] |
| traditional design; single / multi dose: | X | 2 | 2 | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | X | 0 | 0 | Justification for not performing a food-effect study is submitted and reviewed |
| Dissolution: | X | 1 | 1 | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | [redacted] | [redacted] | [redacted] | [redacted] |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | [redacted] | 3 | 2 | |
| | | | | |

| Filability and QBR comments | | |
|---|---|---|
| | "X" if yes | Comments tyo be sent to firm |
| Application filable ? | X | 1. Please submit dissolution data, including dissolution specifications for the proposed Trileptal oral suspension.<br>2. Please submit a table with composition of suspension formulations F3, F4 and F6 and state which of these will be marketed in the U.S.<br>3. A food effect study has not been conducted on the oral suspension; please submit information on the effect of food on the to-be-marketed suspension. |
| Comments sent to firm ? | | |
| QBR questions (key issues to be considered) | 1. Is the proposed Trileptal oral suspension bioequivalent to the marketed tablet, and therefore inter-changeable? | |
| Other comments or information not included above | | |
| Primary reviewer Signature and Date | Vanitha Sekar, PhD | |
| Secondary reviewer Signature and Date | Ramana Uppoor, PhD | |

**CC: NDA 21-285, HFD-850(Lee), HFD-120(Fanari), HFD-860(Sekar, Uppoor, Mehta, Sahajwalla), CDR (B. Murphy)**

# TABLE OF CONTENTS

## OVERALL SUMMARY OF FINDINGS

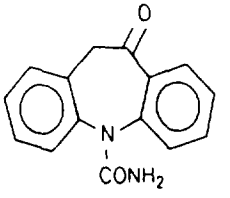
The applicant is seeking approval of oxcarbazepine (Trileptal™) suspension (60 mg/ml) in the USA for oral administration. This submission consists primarily of a BE study comparing the proposed oral suspension to the current approved marketed tablet. The proposed Trileptal oral suspension fails bioequivalence criteria with respect to Cmax when compared to the marketed tablet following a single dose. However, Trileptal is a chronically administered drug and the bioavailability of the suspension and tablet were similar under steady state conditions. Also, pharmacokinetic simulations suggest that the differences in plasma concentrations following switching a subject maintained on tablet at steady – state to the suspension are very small (approximately 7%). Therefore, the suspension and tablet formulations of Trileptal may be used interchangeably. The applicant's proposed dissolution method (USP apparatus 2, paddle speed 75 rpm, 900 ml water with 1% SDS) and dissolution specification ( —— n 30 minutes) for the suspension are acceptable. Food has no effect on the rate and extent of absorption of oxcarbazepine from the approved Trileptal tablets. The bioavailability of the proposed oral suspension is similar to that of the approved tablet formulation under steady state conditions and the proposed suspension and approved tablet can be used interchangeably. Therefore, it is not anticipated that food will have a significant effect on the bioavailability of the proposed suspension.

## INTRODUCTION AND BACKGROUND

Oxcarbazepine (OXC), the keto-analog of carbamazepine, is an orally active anticonvulsant that is presently marketed in the US as 300 and 600 mg film coated tablets. OXC is rapidly reduced by cytosolic enzymes to a monohydroxylated derivative (MHD) which is pharmacologically active.

## CHEMISTRY

The drug substance, OXC (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide), is a tricyclic diarylazepine compound with anticonvulsant activity. OXC is a non-chiral, white to faintly orange crystalline powder with a molecular weight of 252.28. OXC has a $pK_a$ of 10.7 ± 0.2 and a partition coefficient of 1.31 (octanol/phosphate buffer pH 7.4, 25°C). It is slightly soluble in chloroform, dichloromethane, acetone and methanol and practically insoluble in ethanol, ether and water. No polymorphs of the solvent free drug substance have been observed.




## PROPOSED MECHANISM OF ACTION

The anticonvulsant properties of OXC and MHD are possibly mediated by blocking voltage dependant sodium channels, decreasing high voltage activated calcium channels and interaction with potassium channels. The blockade of voltage dependant sodium channels in the brain has been proposed as the most plausible mechanism of action. This is based on results from: 1) in-vitro studies in which OXC and MHD limited sustained high frequency repetitive firing of sodium-dependant action potentials of cultured mouse neurons, and 2) in-vivo study (maximal electroshock) which evaluates the ability of drugs to prevent electrically induced tonic hind limb extension seizures in rodents. Efficacy in the maximal electroshock model has shown to correlate with the ability to prevent partial and generalized tonic-clonic seizures in humans; also drugs that are active in this test (e.g. carbamazepine, phenytoin) often interact with voltage dependant sodium channels.

INDICATION AND PROPOSED DOSAGE AND ADMINISTRATION

Trileptal is recommended for use either as monotherapy (in adults) or in combination with other antiepileptic drugs (in adults and children 4-16 years of age). In mono- and adjunctive therapy, the applicant recommends treatment with Trileptal to be initiated at a dose of 600 mg/day (8-10 mg/kg/day) given in two divided doses. The dose may be increased depending on the clinical response of the patient. Doses of up to 2400 mg/day have been administered in a limited number of patients in order to achieve a maximum therapeutic effect. Drug plasma level monitoring is not a recommendation for Trileptal.

FORMULATION

Composition of to-be marketed suspension formulation F6 of Trileptal

**Table 1.7-3 Composition (per ml) of Trileptal oral suspension (KN 3750510.00.002, KN 3750510.00.004 and KN 3750510.00.006**

| Ingredients | KN 3750510.00.002* (formerly F3) Content (mg) | KN 3750510.00.004 (formerly F4) Content (mg) | KN 3750510.00.006** Content (mg) F6 (to be marketed) |
|---|---|---|---|
| Trileptal/DS extra fine | 60.00 | 60.00 | 60.00 |
| Propyl parahydroxybenzoate; propylparaben | | | |
| Saccharin sodium | | | |
| Sorbic acid | | | |
| Polyethylene glycol 400 stearate | | | |
| Methyl parahydroxybenzoate; methylparaben | | | |
| Ascorbic acid | | | |
| Hydroxyethylcellulose 300 mPas | | | |
| Dispersible cellulose; Microcrystalline cellulose and carboxymethylcellulose sodium | | | |
| Yellow-plum-lemon aroma 20F | | | |
| Yellow-plum-lemon aroma 39K 020 | | | |
| Propylene glycol dist. | | | |
| Sorbitol 70% (non crystallising); sorbitol solution | 2 | 2 | 2 |
| Water purified | | | |
| Total weight | | | |

* Currently marketed formulation in several countries

** Intended commercial formulation. The only differences between the KN 3750510.00.004 and KN 3750510.00.006 formulations is the slight modification to the flavouring agent, addition of less flavouring agent and the consequent compensation by water.

DISSOLUTION

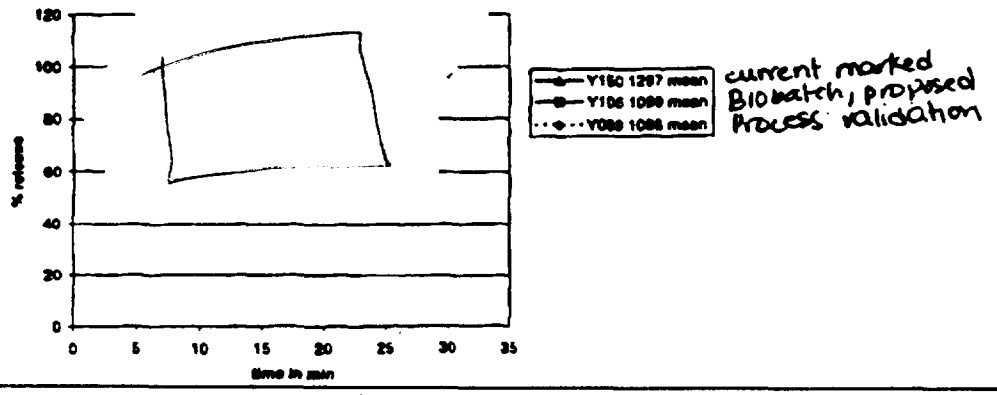
*Has the applicant developed an adequate dissolution method and specifications?*

The sponsor proposed dissolution method and specifications are as follows:

| | |
|---|---|
| Dosage Form: | Suspension |
| Strength: | 60 mg/ml |
| Apparatus Type: | USP Apparatus 2 (paddle) |
| Media: | Water plus 1% Sodium dodecylsulfate (SDS) |
| Volume: | 900 mL |
| Speed of Rotation: | 75 rpm |
| Proposed Dissolution Specification: | —— dissolved in 30 min |

The dissolution specification of —— in 30 min in water plus 1% SDS is acceptable

**Figure 4: Dissolution profile of Trileptal oral suspension batches Y106 1099, Y089 1098 and Y150 1297 at 75 rpm**




BIOAVAILABILITY/BIOEQUIVALENCE

***Is the proposed suspension formulation bioequivalent to the tablet currently marketed in USA?***

- The bioequivalence of Trileptal oral suspension (F6) to the currently marketed tablet (F5) was assessed in healthy volunteers
- The two formulations F6 and F5 fail to meet bioequivalence criteria for Cmax after a single dose
- The two formulations F6 and F5 meet bioequivalence criteria following multiple doses
- Since single dose BE studies are considered most sensitive and are recommended in the General BA/BE guidance, the results indicate that the proposed oral suspension is not bioequivalent to the current marketed tablet

Mean (SD) pharmacokinetic parameters after single doses under fasted conditions

| Formulation | N | AUC (µmol.h/l) | Cmax (µmol /l) | Cmax (µg/ml) | Tmax (h) |
|---|---|---|---|---|---|
| F3, current oral susp., test | 18 | 689 (133) | 34.0 (5.8) | 8.6 (1.5) | 3.5 |
| F6, to-be-marketed oral susp., test | 15 | 656 (122) | 24.9 (6.1) | 6.3 (1.6) | 6 |
| F5, current marketed tablet, reference | 17 | 700 (136) | 31.5 (6.6) | 8.0 (1.7) | 5 |

Estimated ratio and 90% CI after single doses under fasted conditions

| Comparison | Ratio | | 90% CI | |
|---|---|---|---|---|
| | AUC | Cmax | AUC | Cmax |
| F3 vs F5 | 0.97 | 1.03 | (0.99, 1.06); PASS | (0.97, 1.11); PASS |
| *F6 vs F5* | ***0.93*** | ***0.77*** | ***(0.90, 0.97); PASS*** | ***(0.72, 0.82); FAIL*** |
| F6 vs F3 | 0.96 | 0.74 | (0.93, 1.0); PASS | (0.69, 0.79); FAIL |

Mean (SD) pharmacokinetic parameters after multiple doses under fasted conditions

| Formulation | N | AUC (µmol.h/l) | Cmax (µmol /l) | Cmax (µg/ml) | Tmax (h) |
|---|---|---|---|---|---|
| F3, current oral susp., test | 18 | 933 (146) | 91.4 (14.5) | 23.2 (3.7) | 3 |
| F6, to-be-marketed oral susp., test | 15 | 916 (121) | 91.1 (17.9) | 23.1 (4.6) | 4 |
| F5, current marketed tablet, reference | 17 | 900 (137) | 89.4 (12.2) | 22.7 (3.1) | 4 |

Estimated ratio and 90% CI following multiple doses under fasted conditions

| Comparison | Ratio | | 90% CI | |
|---|---|---|---|---|
| | AUC | Cmax | AUC | Cmax |
| F3 vs F5 | 1.03 | 1.00 | (0.99, 1.06) | (0.95, 1.06); PASS |
| ***F6 vs F5*** | ***1.02*** | ***1.01*** | ***(0.99, 1.06)*** | ***(0.95, 1.06); PASS*** |
| F3 vs F6 | 1.00 | 1.00 | (0.96, 1.03) | (0.95, 1.06); PASS |

***Can the proposed suspension formulation be used interchangeably with the current marketed tablet?***

Since the proposed F6 suspension was not shown to be bioequivalent to the marketed tablet following a single dose, the clinical relevance of the differences in Cmax was evaluated. The following two clinical scenarios were considered:

- 1. Impact of starting and maintaining a patient on Trileptal suspension: Trileptal is a titratable drug, therefore, the 20% lower Cmax observed following single dose administration may not be clinically relevant since patients will be titrated to higher doses at weekly intervals if clinical efficacy is not observed. Also, the suspension is bioequivalent to the marketed tablet at steady-state.
- 2. Impact of switching a subject maintained on tablet at steady – state to the suspension: Pharmacokinetic simulations suggest that there is a 7% lower Cmax and about a 4% lower (lesser effect) seizure frequency reduction for the suspension when compared to the tablet (immediately after switching). These differences may not be clinically relevant (discussed with medical officers). See attached Pharmacometrics review for details.
- Therefore, the proposed oral suspension and the approved tablet formulations of Trileptal may be used interchangeably.

## EFFECT OF FOOD

*What is the effect of food on the bioavailability of Trileptal oral suspension and how does it influence dosing recommendations?*

The applicant has submitted a justification for not having conducted a food effect study for the proposed oral suspension.

- absorption is complete following administration of the currently marketed film coated tablet, and this would not change with the oral suspension
- food has no effect on the currently marketed US tablet formulation, and the same extra-fine particles are used in the proposed oral suspension
- the bioavailability of the proposed oral suspension is similar to that of the currently marketed US film coated tablet formulation under steady state conditions
- Although, the suspension is not bioequivalent to the tablet following a single dose, they can be used interchangeably (see above)

For the reasons stated above, the applicant's request for not performing a food effect study is acceptable. The applicant has revised their label to state: "Food has no effect on the rate and extent of absorption of oxcarbazepine from Trileptal tablets. The oral suspension is equally bioavailable to the tablet under fasted conditions, and similarly should be unaffected under fed conditions. Therefore, Trileptal tablets and suspension can be taken with or without food."

LABELING COMMENTS
Please see annotated label with OCPB labeling recommendations (attached).

RECOMMENDATION
The biopharmaceutics information provided in NDA 21-285 is adequate to support the approval of Trileptal oral suspension for the treatment of partial seizures in adults (monotherapy and adjunctive therapy) and in children 4-16 years of age (adjunctive therapy).

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Jogarao Gobburu, Ph.D.
Pharmacometrics Reviewer, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, Ph.D.
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 21-285
/MO/ N. Hershkowitz
/CSO/M. Fanari
/Biopharm/V. Sekar
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta

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Draft Labeling
(not releasable

Trileptal: Assessment of relative bioavailability of 60 mg/ml oral suspension and the current marketed film coated tablets in healthy volunteers

Study# 036 (Item 6 vol. 10)

Principal Investigator: P. Rolan, Medeval, Manchester, UK

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Primary Objective:
To assess the relative bioavailability of the proposed 60 mg/ml Trileptal oral suspension (F6 or F4 variant 006) to the current marketed film coated Trileptal tablet (F5) under fasted conditions following a single dose.

Secondary Objectives:
To assess the relative bioavailability of the proposed 60 mg/ml Trileptal oral suspension (F6 or F4 variant 006) to the current marketed film coated Trileptal tablet (F5) under fasted conditions following multiple doses.

To assess the relative bioavailability of the currently marketed 60 mg/ml Trileptal oral suspension (F3) to the current marketed film coated Trileptal tablet (F5) under fasted conditions following a single dose and under steady state conditions.

To assess the relative bioavailability of the currently marketed (non-US) Trileptal oral suspension (F3) to the proposed 60 mg/ml Trileptal oral suspension (F6) following a single dose and under steady state conditions.

To characterize the single and multiple dose pharmacokinetics of the active metabolite (and the main active moiety), MHD following administration of an oral suspension.

Design:
This was a randomized, open-label, single and multiple-dose, 3-period crossover study in 18 healthy male volunteers (18-45 years) under fasted conditions. During each treatment period, a single 600 mg dose of Trileptal was administered on Day 1 to determine single dose pharmacokinetics over the next 72 hours. On Day 4 onward, until Day 8, Trileptal was administered every 12 hours to determine steady state pharmacokinetics (over the dosing interval of 12 hours) following the oral suspension.

Formulation:
Test product F3: 10 ml of current 60 mg/ml oral suspension of Trileptal (lot Y1501297)
Test product F6: 10 ml of to be marketed 60 mg/ml oral suspension of Trileptal (lot Y1061099)
Reference product F5: 600 mg of current marketed film coated tablet of Trileptal (lot B970119)

Bioanalytical Method:
Plasma samples were analyzed for the active metabolite, MHD using LC/UV methods. The limit of quantification was [redacted] The method was linear in the [redacted]. The precision for QC samples as expressed by %RSD ranged from 5.6% to 7.7% and accuracy for QC samples as expressed by %RE ranged from –1.7% to 2%. The performance of the bioanalytical method for detection of MHD is acceptable. (Plasma concentrations of the parent compound, oxcarbazepine were not measured since it is present in plasma in very low amounts, i.e. <2% of the dose).

**Results:**
Table 1 Composition of to-be marketed 60 mg/mL oral suspension formulation (F6) of Trileptal

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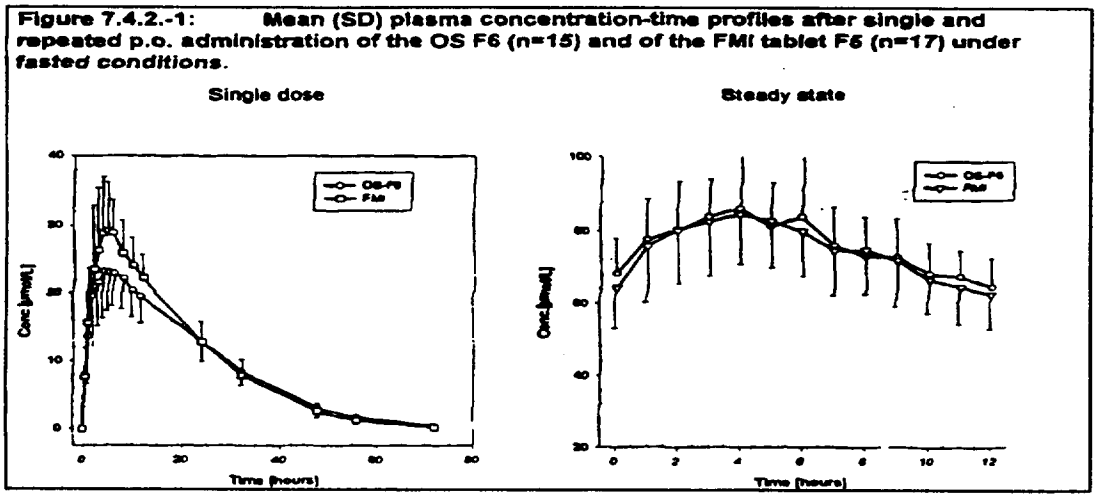
Confidential,
Commercial Information

Figure 1 Mean (SD) MHD plasma concentration vs time under fasted conditions (F6 vs F5)



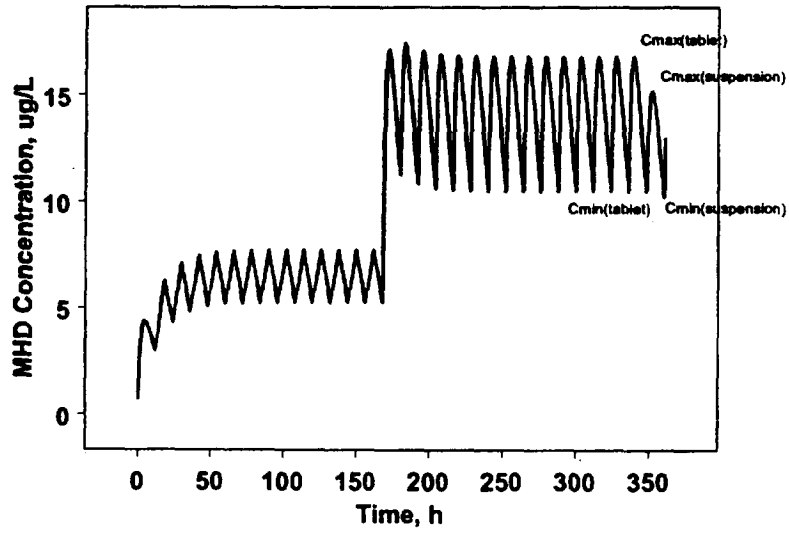

Summary of Results:

1. Following administration of a single dose, the to-be-marketed oral suspension (F6) failed to meet bioequivalence criteria (with respect to Cmax) when compared to the current marketed film coated tablet (F5).
2. Following administration of multiple doses, the to-be-marketed oral suspension (F6) was bioequivalent to the current marketed film coated tablet (F5).
3. Following administration of single and multiple doses, the current oral suspension (F3) was bioequivalent to the current marketed film coated tablet (F5).
4. Following administration of a single dose, the to-be-marketed oral suspension (F6) failed to meet bioequivalence criteria (with respect to Cmax) when compared to the current oral suspension (F3).
5. Following administration of multiple doses, the to-be-marketed oral suspension (F6) was bioequivalent to the current oral suspension (F3).
6. The current oral suspension (F3) has been used in clinical trials in pediatric patients. However, the proposed to-be-marketed (F6) oral suspension has never been used in any clinical trials.

Pharmacokinetic Simulations: The results from this BE study showed that following administration of a single dose, the to-be-marketed oral suspension (F6) failed to meet bioequivalence criteria (with respect to Cmax) when compared to the current marketed film coated tablet (F5). However, following administration of multiple doses, the to-be-marketed oral suspension (F6) was bioequivalent to the current marketed film coated tablet (F5). Trileptal is used as a chronically administered drug, and is unlikely to be used for a single administration. In order to evaluate the clinical relevance of the decreased Cmax for the suspension after a single dose compared to the marketed tablet, the following two clinical scenarios were considered:

1) The impact of starting and maintaining a patient on Trileptal suspension: Trileptal is a titratable drug, therefore, the 20% lower Cmax observed following single dose administration may not be clinically relevant since patients will be titrated to higher doses at weekly intervals if clinical efficacy is not observed. Also, the suspension has similar bioavailability to the marketed tablet at steady-state.
2) The impact of switching a subject maintained on tablet at steady – state to the suspension: Pharmacokinetic simulations were performed using Monte-Carlo simulations. Results from these simulations suggest that there is a 7% lower Cmax (see graph below) and about a 4% lower (lesser effect) seizure frequency reduction for the suspension when compared to the tablet (immediately after switching). These differences may not be clinically relevant (discussed with medical officers). From a purely statistical viewpoint, there appears to be a

high probability (90%) of showing equivalence of the tablet (at steady – state) and suspension (first dose of suspension after achieving steady – state with the tablet) with 16 subjects. The simulated steady state concentrations following administration of the tablet and suspension are approximately 30% lower than those observed in study 036; this is because the initial estimate for Cl/F used for the simulations was obtained from the original NDA for Trileptal and was approximately 30% higher than that observed in study 036. (See attached Pharmacometrics review for details).




Recommendation: The proposed Trileptal oral suspension is not bioequivalent to the current marketed tablet. However, Trileptal is a chronically administered drug and the bioavailability of the suspension and tablet were similar under steady state conditions. Also, pharmacokinetic simulations suggest that the differences in plasma concentrations following switching a subject maintained on tablet at steady – state to the suspension are very small. Therefore, the suspension and tablet formulations of Trileptal may be used interchangeably.

**Trileptal: Effect of food**

The applicant has not conducted a formal food effect study on the proposed oral suspension formulation of Trileptal. At the time of filing of this NDA and in a telecon thereafter, information regarding the effect of food following administration of the oral suspension was requested from the applicant. The applicant has submitted a justification for not having conducted a food effect study for the suspension.

Applicant's justification for lack of a food effect study: There was a significant food effect on the former non-US market tablet formulation (F1, non film-coated 600 mg tablets) of Trileptal (study submitted to original NDA). The applicant states that the in-vitro dissolution for this formulation is incomplete, and the increased bioavailability observed in vivo is due to increased solubility in the presence of food (see table below).

**Table Relative bioavailability of fed vs fasted state (mean(SD); n=6)**

| Compound | AUC Ratio (Fed/Fasted) | AUC 90%CI | Cmax Ratio (Fed/Fasted) | Cmax 90%CI |
|---|---|---|---|---|
| MHD | 1.17 (0.14) | (104%, 129%; FAIL | 1.25 (0.18) | (103%, 141%; FAIL |

**Table Composition of former non-US market formulation) (F1)**

| Component | Quantity (mg) |
|---|---|
| **Core ingredients** | |
| Trileptal | 600.0 |
| Silica, colloidal anhydrous | |
| Hypromellose | |
| Magnesium stearate | |
| Cellulose, microcrystalline | |
| Carmellose, sodium | |
| Iron Oxide, yellow | |
| Core weight | |

Changes were made to the non-US market tablet formulation. The new formulation (F5, film coated 600 mg tablets) is currently marketed in the US. The absolute bioavailability was evaluated for this formulation (submitted to original NDA) and was found to be 99% suggesting complete absorption. There was no effect of food on the bioavailability of the current US formulation (F5) of Trileptal (see table below).

**Estimated ratio and 90% CI (Fed vs. Fasted) following a single dose of 600 mg Trileptal (F5)**

| Compound | Ratio | | 90% CI | |
|---|---|---|---|---|
| | AUC | Cmax | AUC | Cmax |
| **MHD** | 0.98 | 1.12 | (94%, 102%): PASS | (106%, 118%): PASS |

**Composition of the current film coated 600 mg marketed tablet formulation (F5) of Trileptal**

| Ingredient (Core) | Function | Amount per unit (mg) |
|---|---|---|
| OXC | Active | 600 |
| Silica, colloidal anhydrous | Glidant, Antiadherant | ? |
| Crospovidone | Disintegrant | |
| Hypromellose/Hydroxypropyl Methylcellulose/Cellulose HP-M 603 | Binder | |
| Magnesium stearate | Lubricant | |
| Cellulose, microcrystalline | Filler | |
| Water, purified | Granulation fluid | |
| Total | | 600 |
| **Ingredient (coating)** | **Function** | **Amount per unit (mg) 600 mg tablet** |
| Hypromellose/Hydroxypropyl Methylcellulose/Cellulose HP-M 603 | Film forming agent | 1 |
| Ironoxide | Color pigment | |
| Macrogol 8000/PEG 8000 | Plasticizer | |
| Talc | Opacifier, Antiadherant | |
| Titanium dioxide | Pigment, Opacifier | |
| Ethanol with 5% Isopropyl alcohol | Solvent for film coating | |
| Water, purified | Solvent for film coating | |
| Total | | |

The applicant has attributed the lack of a food effect for the currently marketed US formulation to the use of extra-fine particle OXC material in the tablet formulation. The same extra-fine particles are used in the proposed oral suspension.

**Table** **Composition of to-be marketed 60 mg/mL oral suspension formulation (F6 or F4 variant 006) of Trileptal**

**Table 1.7-3** **Composition (per ml) of Trileptal oral suspension (KN 3750510.00.002, KN 3750510.00.004 and KN 3750510.00.006**

| Ingredients | KN 3750510.00.002* (formerly F3) Content (mg) | KN 3750510.00.004 (formerly F4) Content (mg) | KN 3750510.00.006** Content (mg) F6 (to be marketed) |
|---|---|---|---|
| Trileptal/DS extra fine | 60.00 | 60.00 | 60.00 |
| Propyl parahydroxybenzoate; propylparaben | | | |
| Saccharin sodium | | | |
| Sorbic acid | | | |
| Polyethylene glycol 400 stearate | | | |
| Methyl parahydroxybenzoate; methylparaben | | | |
| Ascorbic acid | | | |
| Hydroxyethylcellulose 300 mPas | | | |
| Dispersible cellulose; Microcrystalline cellulose and carboxymethylcellulose sodium | | | |
| Yellow-plum-lemon aroma 20F | | | |
| Yellow-plum-lemon aroma 39K 020 | | | |
| Propylene glycol dist. | | | |
| Sorbitol 70% (non crystallising); sorbitol solution | | | |
| Water purified | | | |
| Total weight | | | |

* Currently marketed formulation in several countries

** Intended commercial formulation. The only differences between the KN 3750510.00.004 and KN 3750510.00.006 formulations is the slight modification to the flavouring agent, addition of less flavouring agent and the consequent compensation by water.

The applicant also states that the proposed oral suspension is bioequivalent to the currently marketed US film coated tablet formulation (under steady state conditions) in their pivotal BE study 036. (Note: Review of this data suggests that the proposed suspension fails to meet bioequivalence criteria following a single dose.) The applicant also cites a prior BE study 034 (this study was repeated due to GCP-related issues with the CRO) in which the suspension (F4; identical to the proposed F6 suspension except for flavoring agent) was bioequivalent to the current marketed US tablet (see table below) following a single dose (see tables below).

***Single dose***

| Formulations | | N | AUC [h(µmol/L)] | $C_{max}$ [µmol/L] | $t_{max}$ [hours] |
|---|---|---|---|---|---|
| F3 OS | Fasted | 16 | 677(100) | 33.0(4.4) | 4 |
| F4 OS | Fasted | 16 | 684(123) | 27.4(6.9) | 5 |
| F5 tablet | Fasted | 16 | 670(132) | 29.8(7.2) | 5 |

Single dose

| Comparison | Parameters | Difference (s.e.) (Log scale) | 90% CI for the Difference (Log scale) | Ratio of means | 90% CI for the ratio |
|---|---|---|---|---|---|
| F3 OS vs. F5 tablet | AUC | 0.0160(0.0247) | (-0.0260, 0.0580) | 1.02 | (0.97, 1.06) |
| F4 OS vs. F5 tablet | | 0.0113(0.0247) | (-0.0307, 0.0534) | 1.01 | (0.97, 1.05) |
| F4 OS vs F3 OS | | -0.0047(0.0247) | (-0.0467, 0.0374) | 1.00 | (0.95, 1.04) |
| F3 OS vs. F5 tablet | $C_{max}$ | 0.1058(0.0438) | (0.0313, 0.1802) | 1.11 | (1.03, 1.20) |
| F4 OS vs. F5 tablet | | -0.1020(0.0438) | (-0.1764, -0.0275) | 0.90 | (0.84, 0.97) |
| F4 OS vs F3 OS | | -0.2077(0.0438) | (-0.2822, -0.1333) | 0.81 | (0.75, 0.88) |

The applicant concludes that food will not affect the bioavailability of the Trileptal oral suspension because: 1) absorption is complete following administration of the currently marketed film coated tablet, and this would not change with the oral suspension, 2) food has no effect on the currently marketed US formulation, and the same extra-fine particles are used in the proposed oral suspension, and 3) the bioavailability of the proposed oral suspension is similar to that of the currently marketed US film coated tablet formulation under steady state conditions (and was found to be bioequivalent under single dose conditions in a prior BE study).

The applicant has proposed a revision to the label from the initial NDA proposal with regard to the effect of food on the bioavailability of the oral suspension.

**Initial NDA proposal:** Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore Trileptal can be taken with or without food.

**Revised proposal:** Food has no effect on the rate and extent of absorption of oxcarbazepine from Trileptal tablets. The oral suspension is equally bioavailable to the tablet under fasted conditions, and similarly should be unaffected under fed conditions. Therefore, Trileptal tablets and suspension can be taken with or without food.

Recommendation: The applicant's request for not performing a food effect study is acceptable since it appears that a food effect is not observed when extra-fine particles of drug substance are used in the formulation.

# Number of Pages Redacted 3

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Confidential,
Commercial Information

**Pharmacometrics Review**

| | |
|---|---|
| NDA: | 21-014 |
| Volume: | 1.11 |
| Compound: | Trileptal |
| Submission Date: | 31 July, 2000 |
| Sponsor: | Novartis Pharmaceuticals Corp., |
| Consult: | Simulations to assess bioequivalence at steady-state |
| pharmacometrics Scientist: | Joga Gobburu |





## Executive Summary

The current review evaluates the impact of switching a subject on tablet at steady – state to a suspension. The Monte-Carlo simulations suggest that there is a 7% lower Cmax and about a 4% lower (lesser effect) seizure frequency reduction for the suspension when compared to the tablet. Whether these differences are of clinical importance needs to be judged by the clinicians. From a purely statistical viewpoint, there appears to be a high probability (90%) of showing equivalence of the tablet (at steady – state) and suspension (first dose after tablet steady – state) with about 16 subjects.

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## Objective

The objective of the review was to assess the impact of switching the formulation from a tablet to suspension at steady – state. Specifically, the difference between the tablet and suspension in terms of the steady – state Cmax and Cmin and its consequence on the seizure frequency reduction.

## Methods

Table 1 shows the values of the parameters together with the justification for their use.

**Table 1. Simulation model specifications and justifications.**

| *Parameter* | *Value* | *Justification* |
|---|---|---|
| *CL/F, L/h* | 3.5 | Estimated using the mean concentration – time data (original NDA) |
| *V/F, L* | 49 | Estimated using the mean concentration – time data (original NDA) |
| *Ka, h*$^{-1}$ | | |
| *Tablet* | 0.5 | Estimated using the mean concentration – time data (study 036) |
| *Suspension* | 0.375 | |
| *Relative Bioavailability* | 0.93 | Estimated tablet/suspension AUC ratio after single-dose (Study 036) |
| *Inter-individual variability* | 15% (CV) | Inter – individual variability of AUC and Cmax at steady – state (see Table 3 (page 8 of PK summary, vol.1 of submission)) |
| *Residual variability (proportional error)* | 10% (CV) | Typical residual variability observed historically. Based on the intra – day precision of the analytical method. |
| *Emax, %* | 69 | Estimated using the dose – response data (study OT/PE1)[a] (see page 2 of the statistics review of the original NDA) |
| *EC50, ng/L* | 43.3 | Estimated using the dose – response data (study OT/PE1)[a] (see page 2 of the statistics review of the original NDA) |
| *Baseline, %* | 7.37 | Estimated using the dose – response data (study OT/PE1)[a] (see page 2 of the statistics review of the original NDA) |

[a] **The OT/PE1 study evaluated the potential of Trileptal as an adjunctive therapy in adults. Concentrations typically achieved at the dose levels were used in the modeling. Though the table in the statistics review indicates a dose of 800 mg/day, the medical review indicates a dose of 600 mg/day, which was used for the present analysis.**

The PK and PD of MHD (pharmacologically active metabolite of oxcarbazepine) were described using a one – compartment model and an Emax model, respectively. Results from study #036 of the current submission were employed to derive the model and the parameters (population means and variances) for the simulations.

The simulations were conducted assuming that each of the subjects received the following treatment:

300 mg tablets b.i.d for 1 week, followed by
600 mg tablets b.i.d for 1 week, followed by
600 mg b.i.d suspension for 1 week.

The trial design included 16 subjects who received the above treatment. The maximum (Cmax) and minimum (Cmin) concentrations on day 14 (last dose of 600 mg tablet) and on day 15 (first

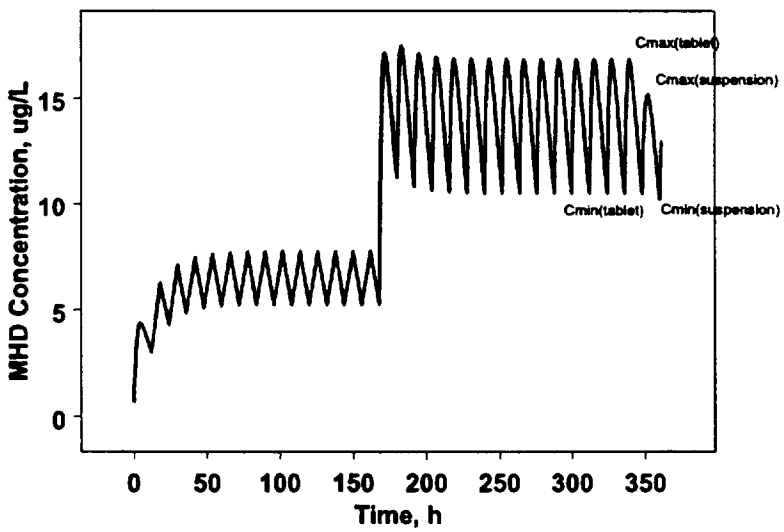
dose of 600 mg suspension) were measured. These measurements will be referred to as Cmax (tablet or suspension) and Cmin (tablet or suspension). The PD effect at the Cmax and Cmin were also estimated 'crudely'. The Cmax and Cmin of the tablet and the suspension were subjected to the bioequivalence testing using the 90% CI approach. The number of replications which showed equivalence of tablet and suspension were counted to determine the probability of establishing bioequivalence ('power') given the trial design.

All simulations were conducted using NONMEM (ver 5.0, level 1.1) and SAS (ver 6.12) was used for the statistical analysis.

## Results and Discussion

Figure 1 shows the typical concentration – time profile obtained in a subject given the dosage regimen described in the methods section. The concentrations achieve steady – state after the 300 and 600 mg tablet dosing in about 50 hours.

Figure 1. Typical (noise-free) MHD concentration – time profile data in a subject receiving 300 mg tablet bid for 1 week, followed by 600 mg tablet bid for 1 week which is followed by 600 mg suspension bid. The Cmin and Cmax for the tablet and suspension are identified on the PK profile.




The concentration - % reduction in seizure frequency relationship is presented in Figure 2. The typical (noise-free) Cmax and Cmin are, 16.84 and 10.50 ug/L for the tablet and 15.9 and 10.22 ug/L for the suspension, respectively. The reduction in the frequency of seizure episodes was determined at the above Cmax and Cmin values. Table 2 shows the summary statistics of the Cmax and Cmin for the tablet and the suspension, and the corresponding PD effect.

**Figure 2. The concentration – effect relationship of MHD. The results from the OT/PE1 study evaluating the potential of Trileptal as an adjunctive therapy in adults were used.**

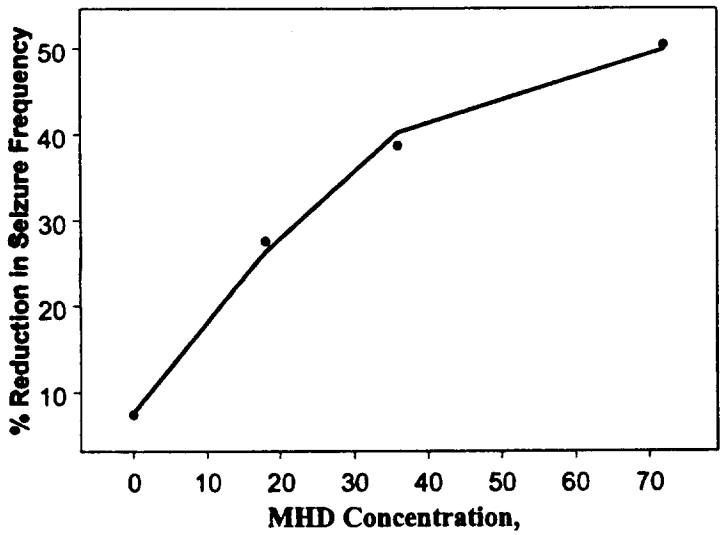



Table 2. Summary of the PK and PD endpoints for the tablet and suspension. The mean and SD were determined from 1000 replicates of simulated data with 16 subjects in each replicate.

| | | PK | | | PD | |
|---|---|---|---|---|---|---|
| Parameter | Formulation | Mean (mg/L) | SD (mg/L) | | Mean (%) | SD (%) |
| **Cmax** | **tablet** | **16.94** | **2.63** | | **26.67** | **2.14** |
| **Cmax** | **suspension** | **15.59** | **2.56** | | **25.53** | **2.18** |
| **Cmin** | **tablet** | **10.75** | **2.29** | | **20.98** | **2.3** |
| **Cmin** | **suspension** | **10.52** | **2.24** | | **20.76** | **2.27** |

Table 3. Probability that the 90% confidence intervals around the ratios of Cmax and Cmin (after logarithmic transformation) of the tablet (reference) and the suspension (test) fall within 80 – 125% limits, determined from 1000 sets of simulated data.

| Parameter | Power | avgLCI | avgRATIO | avgUCI |
|---|---|---|---|---|
| **Cmin** | **96.7** | **0.86** | **0.98** | **1.12** |
| **Cmax** | **84.9** | **0.84** | **0.92** | **1.01** |

**KEY: avgLCI = average lower confidence interval, avgRATIO=average tablet to suspension ratio and avgUCI = average upper confidence interval**

Figure 2 and Table 2 suggest that the differences between the tablet and suspension are relatively small. Theoretically, since a relative bioavailability of 93% (point estimate) was used the difference would be of the same magnitude. Upon switching the formulation from tablet to suspension at steady – state, the concentration would be expected to decrease by 7%. This 7% of difference would remain so through out the dosing, since inherently the relative bioavailability of the suspension is lower than that of the tablet.

The simulations suggest that the Cmin for the tablet is about 10.75 and that for the suspension is about 10.52 mg/L. The corresponding differences in the PD are 27.56 and 27.24%, respectively. From a purely statistical viewpoint, the power to show bioequivalence of the two formulations

(based on the PK parameters reflecting a worst case scenario i.e., last dose of tablet and first dose of suspension) there is a high probability (about 90%) that they are equivalent. Increasing the sample size will simply improve the power. Hence the summary statistics are of major relevance in this case, rather than the issue of power which is merely a design issue answering the question "Should the sponsor conduct a trial with the dosage regimen described in the methods section, what is the probability of establishing bioequivalence between the tablet and suspension?". The summary statistics attempt to answer a difference and more relevant questions, that is, "Should this drug be given to 16 subjects randomly, what are the typical differences in the concentrations and effects?" The simulations demonstrate that if the 600 mg tablet is given to patients then about 27% reduction in seizure frequency can be observed, when compared to baseline. But when switched to the suspension, the reduction in the seizure frequency would be 26%. Hence the extent of bioavailability is more relevant than the rate of bioavailability, since Trileptal is given on a chronic basis. The time to reach the steady – state will not be affected, but the steady – state concentration level will be lower with the suspension by about 7%. These inferences are limited to the scenario tested in the simulations, which assumes a 7% difference in the bioavailability. In fact, the formulations pass the bioequivalence criteria at steady – state. Based on the PD relationship presented in Figure 2 and the summary statistics in Table 2, the clinician should be able to judge if the differences are clinically significant.

The PD analysis is rather crude because the relationship was simply derived using the summary of results from the previous statistics review and the individual data were not used. Consequently, no inter – individual variability in the PD model parameters was considered. Nevertheless, the results give a rough estimate of trends in the PD end point.

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**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| **DATE RECEIVED:** 8/14/00 | **DUE DATE:** 5/4/01 | **OPDRA CONSULT:** 00-0224 |
|---|---|---|

**TO:**

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

**THROUGH:**

Melina Fanari
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

| **PRODUCT NAME:** | **MANUFACTURER:** Novartis |
|---|---|
| Trileptal Oral Suspension (Oxcarbazepine)<br>60 mg/mL<br><br>**NDA #:** 21-285 | |

**SAFETY EVALUATOR:** Jennifer Fan, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a review of the proposed proprietary name "Trileptal Oral Suspension" to determine the potential for confusion with approved proprietary and generic names as well as pending names and for review of labeling and packaging of the product.

**OPDRA RECOMMENDATION:**
OPDRA has no objection to the use of the proprietary name, "Trileptal Oral Suspension". However, OPDRA has concerns with the similarity of labeling between "Trileptal Oral Suspension" and Tegretol Suspension, both labeled by Novartis. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approval of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3242
Fax: 301-480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm. 15B03**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** May 2, 2001

**NDA NUMBER:** 21-285

**NAME OF DRUG:** Trileptal Oral Suspension (Oxcarbazepine), 60 mg/mL

**NDA HOLDER:** Novartis

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the tradename "Trileptal Oral Suspension" and for the safety review of the container labels, labeling and packaging, and package insert. The proprietary name, Trileptal, has already been on the U.S. market since January 14, 2000.

PRODUCT INFORMATION

Trileptal is an antiepileptic drug that is already available as 150-mg, 300-mg, and 600-mg tablets. The sponsor is now making available "Trileptal Oral Suspension". Trileptal is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy. The "Trileptal Oral Suspension" is available as a 60-mg/mL concentration in a net volume of 250 mL.

## II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Trileptal Oral Suspension" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches.

### A. EXPERT PANEL DISCUSSION

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[5] WWW location http:// www.uspto.gov/tmdb/index.html.

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Trileptal Oral Suspension". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Since Trileptal tablets were approved on January 14, 2000, the Expert Panel had concerns on whether or not there has been any confusion problems with the tablets. One concern was the potential of similar packaging with Tegretol Suspension. The Panel did not report any other sound-alike and/or look-alike name potentials and had no objections to the name "Trileptal Oral Suspension" since Trileptal tablets are already on the U.S. market.

Table 1

| | | | |
|---|---|---|---|
| Tegretol Suspension | Carbamazepine<br>(Antiepileptic – Rx)<br><br>Suspension (Oral): 100 mg/5 mL (total volume in bottle: 450 mL) | 100 mg (1 tsp) four times a day. | S/A, L/A per OPDRA |
| | | *Frequently used, not all-inclusive | **S/A(Sound-alike), L/A (Look-alike |

AERS Search

Since Trileptal is an approved product, searches in the *Adverse Event Reporting System* (AERS) were conducted for any post-marketing safety reports of medication errors associated with Trileptal. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, "Trileptal%" and "oxcarbazepine%" were used to perform the searches.

The search in AERS only yielded one medication error report (ISR 3539672-2) submitted on July 18, 2000. In this event, the retail pharmacist was presented a written prescription for Trileptal. The patient, who had received Lamictal (lamotrigine) before, received Lamictal 150 mg instead of Trileptal 300 mg. According to the medication error report, the patient was allegedly sent to the emergency room. According to the reporter, the pharmacist had mistakenly filled the prescription with the wrong medication due to distractions (conversing with the patient at a busy period of time) and associating the patient with a prior treatment with Lamictal.

B. SAFETY EVALUATOR RISK ASSESSMENT

Since January 14, 2000, the proprietary name, Trileptal, has been in the U.S. market with only one medication error report on the confusion between Lamictal and Trileptal. The confusion between Trileptal and Lamictal was probably not due to label and name confusion since other factors were involved such as patient prior treatment. The potential risk of confusion between Lamictal and "Trileptal Oral Suspension", is low since Lamictal is available in tablet (25 mg, 100

mg, 150 mg, 200 mg) and chewable tablet (2 mg, 5 mg, 25 mg) dosage form while "Trileptal Oral Suspension" is in a liquid form (60 mg/mL in 250 mL).

However, there is a concern that "Trileptal Oral Suspension" can be confused with Tegretol Suspension since the name looks somewhat similar on the label and the label design is similar. Tegretol Suspension, 100 mg/5 mL, is available in a 450 mL container while Trileptal Oral Suspension is available in a 250 mL container. The width and the height of the labels are also different. Since label designs are similar, the Trileptal Oral Suspension could be mistaken as a lower volume of the Tegretol Suspension. Even if Trileptal Oral Suspension is kept in the carton, it may still be mistaken as a lesser volume of Tegretol Suspension due to the similarity in design style (color of packaging and lettering and placement of information) on the carton labeling. Also, both products would be in the same area, the same shelf in the pharmacy. This may create a potential risk of medication errors. Please see below for labeling recommendations.

There is a similarity between the established names of Trileptal and Tegretol, oxcarbazepine and carbamazepine. This would pose a problem when the generics of these brands become available in the U.S. market.

Since "Trileptal Oral Suspension" is only a different dosage form with the same active ingredient as Trileptal tablets, OPDRA has no objections to the name "Trileptal Oral Suspension".

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL and CARTON LABELING (60 mg/mL, 250 mL)

1. Since the design of the container label is similar to Tegretol Suspension, 100 mg/5 mL, the proprietary name, Trileptal, should be highlighted by a different color so that it is differentiated from the proprietary name, Tegretol.

2. The sponsor has proposed to label the concentration as in milliliters (60 mg/mL). The conventional method for strength expression for oral liquids is mg/5 mL. Concentrated liquids are usually expressed as mg/mL. Since the dose of this product will be greater than 1 mL, as evidenced by the package insert and the 10 mL oral syringe, please express the strength as 300 mg/5 mL.

B. PACKAGE INSERT AND PATIENT INFORMATION INSERT (60 mg/mL, 250 mL)

1. No comments.



## IV. RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name "Trileptal Oral Suspension".

   OPDRA has no objections to the use of the proprietary name "Oral Suspension". OPDRA considers this a final review due to the primary goal date of May 31, 2001. OPDRA has no objections to the use of the proprietary name "Trileptal Oral Suspension".

3. OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Jennifer Fan
5/4/01 04:31:14 PM
PHARMACIST

Jerry Phillips
5/7/01 08:52:52 AM
DIRECTOR

Martin Himmel
5/7/01 11:17:34 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Date: 5/10/01 9:02:44 AM
From: Lisa Stockbridge ( STOCKBRIDGEL )
Subject: Trileptal Instructions
Melina Fanari ( FANARIM )

Melina,

Here are the edits on the instructions.

Lisa

APPEARS THIS WAY
ON ORIGINAL

**Trileptal (oxcarbazepine) Oral Suspension**

**Instructions for Use**

Read these instructions carefully to learn how to use the medicine dispensing system correctly.

## The Medicine Dispensing System

There are 3 parts to the dispensing system:

1. A **plastic adapter** that you push into the neck of the bottle the first time that you open the bottle. The adapter must always stay in the bottle.
2. A **bottle** containing 250 mL of the medicine, with a child resistant cap. Always replace the cap after use.
3. A 10 mL **oral dosing syringe** that fits into the plastic adapter to withdraw the prescribed dose of medicine from the bottle.

## Preparing the Bottle

1. Shake the bottle of medicine for **at least 10 seconds**. [*Why is shaking needed here? See Step 1 below]*
2. Remove the child resistant cap by pushing it **firmly** down and turning it counterclockwise—to the left (as shown on the top of the cap).

**Note**: Save the cap so you can close the bottle after each use.

3. Hold the open bottle upright on a table and push the plastic adapter **firmly** into the neck of the bottle as far as you can.
4. **Replace the cap to be sure that the adapter has been fully forced into the neck of the bottle**.

**Note**: You may not be able to push the adapter fully down, but it will be forced into the bottle when you screw the cap back on.

Now the bottle is ready to use with the syringe

## Taking the Medicine

1. Shake the bottle well. Prepare the dose right away.
2. Push and turn the child resistant cap to open the bottle.

**Note**: Always replace the cap after use.

*[The figure for instruction 4 should label the barrel and the plunger]*

3. Check that the plunger is all the way down inside the barrel of the syringe.
4. Keep the bottle upright and push the syringe **firmly** into the plastic adapter.
5. Hold the syringe in place and carefully turn the bottle upside down.
6. Slowly pull the plunger out so that the syringe fills with some medicine. Push the plunger back in just far enough to completely push out any large air bubbles that may be trapped in the syringe.
7. Slowly pull the plunger out until the top edge of the black ring is exactly level with the marker on the syringe barrel for the prescribed dose.

*[Diagram associated with 7 should say "dose," not "your dose."]*

**Note:** If the prescribed dose is more than 10 mL, you will need to reload the syringe to make up the full dose.

8. Carefully turn the bottle upright. Take out the syringe by gently twisting it out of the plastic adapter. The plastic adapter should stay in the bottle.

9. You can mix the dose of medicine in a small glass of water before it is swallowed, or you can drink it directly from the syringe.
   a. **If you mix the medicine with water**, add some water to a glass. Push in the plunger on the syringe all the way to empty all the medicine into the glass. Stir the medicine in the water and drink it all.
   b. **If you use the syringe to take the medicine**, the patient must sit upright. Push the plunger **slowly** to let the patient swallow the medicine.

10. Replace the child resistant cap after use.

**Cleaning:** After use, rinse the syringe with warm water and allow it to dry.

## CDER LABELING AND NOMENCLATURE COMMITTEE

| CONSULT # | 1041 | HFD# | 120 | PROPOSED PROPRIETARY NAME: | PROPOSED ESTABLISHED NAME: |
|---|---|---|---|---|---|
| ATTENTION: | MELINA MALANDRUC | | | TRILEPTAL | Oxcarbazepine Film-Coated Tablets, 150 mg and 300 mg, 600 mg |

**A. Look-alike/Sound-alike**

| | Potential for confusion: |
|---|---|
| TRIAVIL | XXX Low ____ Medium ____ High |
| TRILEVLEN | XXX Low ____ Medium ____ High |
| PLETAL | XXX Low ____ Medium ____ High |
| | ____ Low ____ Medium ____ High |
| | ____ Low ____ Medium ____ High |

**B. Misleading Aspects:**

**C. Other Concerns:**

**D. Established Name**

____ Satisfactory

XXX Unsatisfactory/Reason

"FILM-COATED" SHOULD NOT BE INCLUDED IN THE NAME

Recommended Established Name

OXCARBAZEPINE TABLETS

**E. Proprietary Name Recommendations:**

XXX ACCEPTABLE ____ UNACCEPTABLE

**F. Signature of Chair/Date** /S/