CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-911

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: September 19, 2008

FROM: David J. Claffey, PhD

SUBJECT: **Office of Compliance recommendation for NDA 21-911**
NDA 21-911 INOVELON (rufinamide) tablets

The CMC review (11 SEP 2006) for NDA 21-911 recommended that this application be approved. During the first review cycle the Office of Compliance made an overall acceptable recommendation (22 JUN 2006). As Agency action on this Application appeared likely to be more than 24 months after the initial OC recommendation, a second establishment evaluation request was made at the beginning of this review cycle. The OC provided an overall acceptable recommendation on 18 SEP 2008. An approval recommendation can once again be made from a CMC perspective for this application.

Appears This Way
On Original

MEMORANDUM

To: NDA 21-911
From: Chi-wan Chen, Acting Director, Division of Pre-Marketing Assessment I
Date: September 11, 2006
Subject: Executive Summary for NDA 21-911, Trade Name (rufinamide) Tablets, 100, 200 and 400 mg.

Introduction: Trade Name (rufinamide) tablets, submitted under Eisai's NDA 21-911, are indicated for the adjunctive treatment of partial seizures with and without secondary generalization in adults and adolescents 12 years of age and older. Additionally, it is also indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in adults and in children 4- —years old. The packaging in HDPE bottles of various sizes for [redacted] and the commercial product (30, [redacted] tablet count) is proposed, [redacted] The trade name, Inovelon, proposed by the applicant is currently under review by DMETS. The applicant has provided an environmental assessment in the submission. The environmental assessment reviewer has completed the review with "findings of no significant impact". b(4)

Drug Substance:

The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. It is insoluble in water, regardless of pH; slightly soluble in methanol and THF and sparingly soluble in ethanol and acetonitrile. Rufinamide consistently crystallizes as low-density or 'fluffy' needle-shaped particles. These particles have a tendency to agglomerate. [redacted]

[redacted] b(4)

[redacted] b(4)

Drug Product: The drug product consists of pink-colored ovaloid tablets with a score. The functionality of the score is supported by the weight uniformity and dissolution data. A post-approval commitment to carry out a two week stability study of the split tablets was provided by the applicant. This is acceptable based on the fact that the drug product has proved very stable even at high temperature and humidity. Moreover, un-coated tablets were used in clinical studies without any stability issues. Each of the three strengths shares a common composition, only the tablet weight differs. The excipients are typical for an immediate-release tablet, with rufinamide contributing to [redacted] A pink film-coat is applied to all three strengths of the tablets to mask the slight bitter taste of rufinamide. The drug product is manufactured by a [redacted] The proposed dissolution test has two different time points for each strength: [redacted] dissolution must occur after four to six hours and [redacted] dissolution must occur within 10 to 16 hours, depending on the strength. This is consistent with the low solubility of the drug substance. The in vivo data show that Cmax is generally achieved after ca. 3 hours. The stability studies demonstrated that rufinamide is very stable. The two impurities detected being the process impurities which are adequately controlled. The provided stability data support the proposed 36 month expiry period for the drug product.

b(4)

Recommended action: An "Approval" recommendation is being made by the CMC reviewer based on all the CMC information provided in the original submission and subsequent response to our information request. An overall acceptable recommendation was made by the Office of Compliance for the facilities involved in the manufacture of drug substance and drug product.

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/s/

Ramesh Sood
9/11/2006 07:48:40 AM
CHEMIST

Chi Wan Chen
9/11/2006 11:01:20 AM
CHEMIST

NDA 21-911

INOVELON
(rufinamide) Tablets

Eisai Inc

David J. Claffey, Ph.D.

ONDQA

For
Division of Neurology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-911

2. REVIEW #:1

3. REVIEW DATE: 8 September 2006

4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N 21-911 N-000 (original application)	8-SEP-2005
N 21-911 (C)	5-OCT-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N 21-911 N-000 (RS)	17-NOV-2005
N 21-911 N-000 (BZ) (revised DS specification)	23-MAY-2006
N 21-911 (N-000 (BC) (validation of DS production)	15-JUN-2006
N 21-911 (N-000 (BC) (response to IR)	1-SEP-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Eisai Medical Research Inc.

Chemistry Review Data Sheet

Address:	55 Challenger Road, Ridgefield Park, NJ 07660
Representative:	Loretta Robertson, Pharm.D.
Telephone:	(201) 403 2659

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: INOVELON Tablets
b) Non-Proprietary Name (USAN): rufinamide
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Treatment of partial seizures and for seizures associated with Lennox-Gastaut Syndrome

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 100, 200 and 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN: Rufinamide

Chemical Name(s)

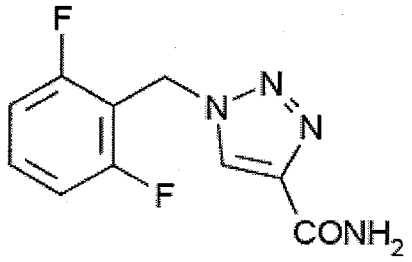
IUPAC: 1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide

CAS: 1-[(2,6-Difluorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide

CAS#: 106308-44-5

Research Codes CGP 33101; RUF 331

US Adopted Name (USAN) RUFINAMIDE



Molecular formula $C_{10}H_8F_2N_4O$

Relative molecular mass 238.2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

b(4)

Chemistry Review Data Sheet

	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	
	III		4	Adequate	

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	35,534	Treatment of seizures with rufinamide

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	22 JUN 2006	S Adams
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Submission of MVP to DPA is not recommended		
DMETS	Pending		
EA	FONSI	8-SEP-2006	Ruth Gaginus, PhD
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-911

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from a chemistry perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This application proposes the marketing of INOVELON (rufinamide) Tablets for the treatments of partial seizures and for seizures associated with Lennox-Gastaut Syndrome. Marketing of immediate-release orally-administered film-coated tablets of three strengths (100 mg, 200 mg and 400 mg) is proposed. Packaging in HDPE bottles of various sizes for t) and the commercial product (30, tablet count) is proposed, b(4)

The drug substance, rufinamide, is a 'new molecular entity'. It is insoluble in water, regardless of pH; it is slightly soluble in methanol and THF and sparingly soluble in ethanol and acetonitrile. Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide. It has an empirical formula of $C_{10}H_8F_2N_4O$ and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Given the relatively small size of this molecule, its chemical characterization was through and indisputable. However, its physical characterization was rather more complex in two respects. Firstly, rufinamide consistently crystallizes as low-density or needle-shaped particles. Secondly these particles have a tendency to agglomerate.

b(4)

b(4)

Whereas Cmax is generally achieved after ca. 3 hours, the proposed dissolution test has two different time points for each strength: dissolution must occur after four to six hours and , dissolution must occur within 10 to 16 hours, depending on the strength. Therefore the proposed dissolution specification is regarded as being a quality control test only. The two time points and the long time that will be allowed for *in vitro* dissolution is unusual for a supposed immediate-release drug, however its *in vivo* dissolution is much faster and the proposed limits will ensure that future drug product lots dissolve within a reasonable time. It should be noted that he biopharm reviewer is satisfied with the proposed dissolution test and limits

b(4)

b(4)

The drug product consists of pink-colored ovaloid tablets with a score. Each of the three strengths share a common composition, only the tablet weight differs. The excipients are typical for an immediate-release tablet, with rufinamide contributing A pink film-coat is applied to the tablets to mask the slight bitter taste of rufinamide. The drug product is manufactured by at . Early in development the formulations containing between 1 and 200 mg were manufactured by

and were film-coated to mask the slightly bitter taste of the drug substance. The final tablet shape was changed from ovaloid and a score was added to facilitate splitting. A detailed listing of the formulations used for each clinical study was provided in the application (3.2.P.2.1 Attachment 2.2.A1). The applicant states that a series of

bioequivalency studies (#015, 036 and 037) established the equivalence of earlier formulations and processes with the proposed commercial formulation and process. Stability studies demonstrated rufinamides stability, the only two impurities detected being two process impurities which are adequately controlled. Stability data support the proposed [redacted] for the drug substance and the 36 month expiry period for the drug product. b(4)

B. Description of How the Drug Product is Intended to be Used

The following is the proposed dosing regime which is dependant on patient age and indication:

1. [redacted] b(4)

2. For adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4- [redacted] years, it is proposed to initiate treatment at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a [redacted] of 45 mg/kg/day or 3200 mg/day whichever is less, administered in two equally divided doses. For adults it is proposed that treatment be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg/day every 2 days until [redacted] a maximum daily dose of 3200 mg/day, administered in two equally divided doses is reached. b(4)

   Drug product expiry period is 36 months.

C. Basis for Approvability or Not-Approval Recommendation

The approval recommendation was based on the following:

- The drug substance and drug product specifications together with the in process controls and extensive stability data will adequately ensure continued product quality through the expiry period.

- Adequate response to the information request of 24 AUG 2006.

- An overall acceptable recommendation was received from the Office of Compliance.

- The FONSI recommendation from the environmental assessment reviewer.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

110 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

David Claffey
9/8/2006 02:19:27 PM
CHEMIST

Ramesh Sood
9/11/2006 07:39:54 AM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	21-911
Applicant:	Eisai Medical Research, Inc.
Stamp Date:	17-Nov-2005
PDUFA Date:	17-Sep-2006
Trademark:	Inovelon®
Established Name:	rufinamide
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Adjunctive treatment of partial seizures; adjunctive treatment of seizures associated with Lennox-Gastaut syndrome
PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

Summary

Rufinamide (chemical name: 1-[(2,6-Difluorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide) is a neutral, small molecule NCE that was originally developed by Novartis for use as an anticonvulsant. Novartis discontinued development in 2001 and Eisai acquired development rights in May 2004. Although no formal CMC pre-NDA meeting was held, Eisai submitted a stability proposal and protocol in August 2004 (IND 35,534, Ser. No. 177). The firm's proposal, which was accepted by the Agency, provided for a reduced (bracketed/matrixed) stability protocol and the submission of the following:

- a full ICH stability package from Novartis for drug substance and drug product
- analytical results for the three Eisai full scale production validation batches of drug substance and drug product
- identification of any changes to the in-process controls
- comparative dissolution profiles and corresponding f2 values of Novartis and Eisai manufactured drug product
- certification of successful completion of the validation process to be submitted at least three months before the PDUFA decision date

1 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

Drug substance impurities: The proposed maximum dose is 3200 mg/day. The applicant acknowledges that the ICH reporting and identification thresholds are 0.03% and 0.05%, respectively; but proposes a limit of NMT for any unspecified impurity. The ICH qualification threshold is also 0.05% for a daily intake greater than 2000 mg. The limit would allow for unspecified impurities to exceed the qualification threshold. It also not clear that the firm's analytical methods are r impurity levels as the quantitation limit is stated to be

b(4)

b(4)

Linkage between clinical drug product batches (manufactured by and commercial product

Examination of the adequacy of technology transfers, i.e., transfer of the final stages of drug substance manufacture from Novartis to and transfer of tablet manufacture from Novartis to Eisai is recommended.

Comments for 74-Day Letter

The following may be considered by the reviewer for inclusion in the 74-day letter:

With regard to drug substance impurities, you propose maximum dose of 3200 mg rufinamide per day. ICH reporting, identification and qualifications for a daily intake greater than 2000 mg are 0.03%, 0.05% and 0.05%, respectively. As you propose a limit for individual unspecified impurities the qualification threshold additional justification may be required. We also note that the quantitation limit for your analytical method is stated to be which does not appear adequate for quantitation impurities at the reporting threshold.

b(4)

D. Review, Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. As discussed above, the most critical aspects of this submission relate to physical properties of the drug substance. Given the interrelationship between the drug substance physical properties and product manufacturability and performance it is recommended that a single reviewer be assigned to review the NDA, with a possible consultation for review of the tablet dissolution test procedure.

Recommended reviewer: David Claffey

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead

December 14, 2005
Date

Ramesh Sood, Ph.D.
Branch Chief

December 15, 2005
Date

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/s/

Martha Heimann
12/15/2005 11:00:32 AM
CHEMIST

Ramesh Sood
12/15/2005 12:00:55 PM
CHEMIST