

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202834Orig1s000**

**CHEMISTRY REVIEW(S)**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Application:** NDA 202834/000  
**Code:** 120  
**Priority:** 1  
**Stamp Date:** 25-MAY-2011  
**PDUFA Date:** 22-OCT-2012  
**Action Goal:**  
**District Goal:** 23-AUG-2012

**Sponsor:** EISAI INC  
 155 TICE BLVD  
 WOODCLIFF LAKE, NJ 07677  
**Brand Name:** FYCOMPA (PERAMPANEL)

**Estab. Name:**  
**Generic Name:**

**Product Number; Dosage Form; Ingredient; Strengths**

001; TABLET; PERAMPANEL; 2MG  
 002; TABLET; PERAMPANEL; 4MG  
 003; TABLET; PERAMPANEL; 6MG  
 004; TABLET; PERAMPANEL; 8MG  
 005; TABLET; PERAMPANEL; 10MG  
 006; TABLET; PERAMPANEL; 12MG

<b>FDA Contacts:</b>	T. BOUIE	Project Manager	3017961649
	L. SOLDATOVA	Review Chemist	3017961758
	M. HEIMANN	Team Leader	3017961678

<b>Overall Recommendation:</b>	ACCEPTABLE	on 10-OCT-2012	by R. SAFAAI-JAZI	( )	3017964463
	PENDING	on 04-JAN-2012	by EES_PROD		
	PENDING	on 04-JAN-2012	by EES_PROD		
	PENDING	on 03-JUN-2011	by EES_PROD		

**Establishment:** CFN: (b) (4) FEI: (b) (4)



**DMF No:**  
**Responsibilities:**  
**Profile:**  
**AADA:**  
**OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 06-JAN-2012  
**Decision:** ACCEPTABLE  
**Reason:** BASED ON PROFILE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 9614628 FEI: 3002806886  
EISAI CO LTD  
KASHIMA-KEN, IBARAKI, JAPAN

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Profile:** NON-STERILE API BY (b)(4) OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 06-JAN-2012

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** CFN: FEI: 3003404441  
EISAI CO., LTD.  
1 KAWASHIMATAKEYA-MACHI  
KAKAMIGAHARA-SHI, GIFU, JAPAN

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** TABLETS, PROMPT RELEASE OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 10-OCT-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 1063718 FEI: 3001753294  
EISAI INC

RESEARCH TRIANGLE PARK, , UNITED STATES 27709

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 05-OCT-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 17-JAN-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Application:** NDA 202834/000  
**ip Date:** 25-MAY-2011  
**Regulatory:** 22-OCT-2012

**Action Goal:**  
**District Goal:** 23-AUG-2012

**Applicant:** EISAI INC  
155 TICE BLVD  
WOODCLIFF LAKE, NJ 07677

**Brand Name:** FYCOMPA (PERAMPANEL)  
**Estab. Name:**  
**Generic Name:**

**Priority:** 1  
**Org. Code:** 120

**Product Number; Dosage Form; Ingredient; Strengths**

001; TABLET; PERAMPANEL; 2MG  
002; TABLET; PERAMPANEL; 4MG  
003; TABLET; PERAMPANEL; 6MG  
004; TABLET; PERAMPANEL; 8MG  
005; TABLET; PERAMPANEL; 10MG  
006; TABLET; PERAMPANEL; 12MG

**Application Comment:** THIS IS A NME. THE APPLICATION CONTACT PERSON IS HEATHER BRADLEY, 201-949-4691 (on 02-JUN-2011 by D. HENRY () 3017964227)  
CONTACT ONDQ REVIEWER LYUDMILA SOLDATOVA FOR PARTICIPATION ON THE INSPECTION (on 03-JUN-2011 by D. HENRY () 3017964227)  
NDA RESUBMITTED ON 12/22/2011 (on 04-JAN-2012 by M. HEIMANN () 3017961678)

<b>FDA Contacts:</b>	T. BOUIE	Project Manager	3017961649
	L. SOLDATOVA	Review Chemist	3017961758
	M. HEIMANN	Team Leader	3017961678

---

<b>Overall Recommendation:</b>	ACCEPTABLE	on 10-OCT-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 04-JAN-2012	by EES_PROD		
	PENDING	on 04-JAN-2012	by EES_PROD		
	PENDING	on 03-JUN-2011	by EES_PROD		

---

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)  
 (b) (4)

DMF No: AADA:  
 Responsibilities: (b) (4)

Establishment Comment: Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-JUN-2011				HENRYD
OC RECOMMENDATION	08-JUN-2011			ACCEPTABLE BASED ON PROFILE	STOCKM
REQUEST CANCELLED	21-JUL-2011			REFUSE TO FILE	BOUIET
SUBMITTED TO OC	04-JAN-2012				HEIMANNM
OC RECOMMENDATION	06-JAN-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9614628 FEI: 3002806886  
 EISAI CO LTD  
 KASHIMA-KEN, IBARAKI, JAPAN

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE PACKAGER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

**Establishment Comment:** MANUFACTURING INCLUDING (b) (4) PACKAGING, RELEASE TESTING,  
 STABILITY TESTING OF DRUG SUBSTANCE (on 03-JUN-2011 by D. HENRY () 3017964227)  
**Profile:** NON-STERILE API BY (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-JUN-2011				HENRYD
SUBMITTED TO DO	08-JUN-2011	Product Specific			STOCKM
DO RECOMMENDATION	16-JUN-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	16-JUN-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
REQUEST CANCELLED	21-JUL-2011			REFUSE TO FILE	BOUIET
SUBMITTED TO OC	04-JAN-2012				HEIMANNM
OC RECOMMENDATION	06-JAN-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** **CFN:** FEI: 3003404441  
EISAI CO., LTD.  
1 KAWASHIMATAKEYA-MACHI  
KAKAMIGAHARA-SHI, GIFU, JAPAN

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

**Establishment Comment:** CONTACT ONDQ REVIEWER LYUDMILA SOLDATOVA FOR PARTICIPATION ON THE INSPECTION (on 03-JUN-2011 by D. HENRY () 3017964227)  
MANUFACTURE (BULK TABLETS), BULK PACKAGING, QUALITY CONTROL, RELEASE TESTING OF DRUG PRODUCT (on 03-JUN-2011 by D. HENRY () 3017964227)

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-JUN-2011				HENRYD
SUBMITTED TO DO PLEASE CONTACT ONDQA REVIEW TEAM FOR INSPECTION PARTICIPATION	08-JUN-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	16-JUN-2011	Product Specific			PHILPYE
INSPECTION PERFORMED AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED	16-JUN-2011				FACTS_EES
ASSIGNED INSPECTION TO IB	07-JUL-2011	Product Specific			STOCKM
REQUEST CANCELLED	21-JUL-2011			REFUSE TO FILE	BOUIET
SUBMITTED TO OC	04-JAN-2012				HEIMANNM
SUBMITTED TO DO	06-JAN-2012	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	21-JAN-2012	GMP Inspection			PHILPYE
ASSIGNED INSPECTION TO IB TO MAKE IT PS+GMP	05-APR-2012	Product Specific			PHILPYE
INSPECTION PERFORMED This was a pre-announced Pre-Approval and GMP inspection of a Bulk finished product manufacturer conducted in response to an EES request for a Pre-approval Inspection/Investigations for NDA 202-834 for manufacture of Fycompa (Perampanel) 2, 4, 6, 8, 10 and 12 mg tablets. The inspection was conducted in accordance with Compliance Programs: 7356.002, Drug Manufacturing Inspections (PAC 56002), and 7346.832, Pre-Approval Inspections (PAC 46832). The GMP portion of the inspection covered the following: Quality, Facilities/Equipment and included profile classes CHG and TCM. FACTS assignment # 7126133.  The previous GMP inspection conducted in (b) (4) had no deficiencies resulting in an FDA-483. Minor deficiencies were noted.  The current inspection verified the corrective actions for the minor deficiencies from the previous inspection (09/2009) and found them adequately implemented. Refer under "Voluntary Correction" caption. Current inspection had no new deficiencies. No FDA-483 was issued, no samples were collected, and there were no refusals.	26-APR-2012	26-APR-2012		LUCAS.LEAKE	
DO RECOMMENDATION	09-OCT-2012			ACCEPTABLE	PHILPYE

October 10, 2012 4:04 PM

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

INSPECTION

OC RECOMMENDATION

10-OCT-2012

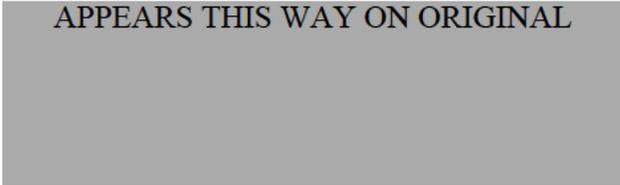
ACCEPTABLE

SAFAAIJAZIR

DISTRICT RECOMMENDATION

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APPEARS THIS WAY ON ORIGINAL



**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 1063718 FEI: 3001753294  
EISAI INC  
900 DAVIS DRIVE  
RESEARCH TRIANGLE PARK, NC 27709

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:** FINAL PACKAGING, QUALITY CONTROL, RELEASE TESTING, STABILITY TESTING OF DRUG PRODUCT (on 03-JUN-2011 by D. HENRY () 3017964227)  
FINAL PACKAGING, QUALITY CONTROL, RELEASE TESTING, STABILITY TESTING OF DRUG PRODUCT (on 03-JUN-2011 by D. HENRY () 3017964227)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE  
TABLETS, PROMPT RELEASE NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-JUN-2011				HENRYD
SUBMITTED TO DO	08-JUN-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	05-JUL-2011	Product Specific			JCHANCEY
INSPECTION SCHEDULED	05-JUL-2011		15-JUL-2011		JCHANCEY
REQUEST CANCELLED	21-JUL-2011			REFUSE TO FILE	BOUIET
SUBMITTED TO OC	04-JAN-2012				HEIMANNM
SUBMITTED TO DO	06-JAN-2012	Product Specific			INYARDA
DO RECOMMENDATION	05-OCT-2012			ACCEPTABLE	JCHANCEY
<p>THE MOST RECENT INSPECTION OF THIS FACILITY TOOK PLACE (b) (4) RESULTED IN THE ISSUANCE OF AN 8-POINT FDA-483, AND WAS CLASSIFIED VAI. CITATIONS FROM THE INSPECTION INCLUDED: INADEQUATE PROCEDURES FOR (b) (4), FAILURE TO CONDUCT THOROUGH INVESTIGATIONS INTO (b) (4) EVENTS; FAILURE TO CONDUCT INVESTIGATIONS INTO UNEXPLAINED DISCREPANCIES RELATED TO (b) (4) EVENTS; INADEQUATE STABILITY PROTOCOLS FOR AN INJECTABLE PRODUCT; INADEQUATE WRITTEN PROCEDURES FOR (b) (4) INTEGRITY TESTING; LACK OF WRITTEN PROCEDURES APPLICABLE TO THE QUALITY CONTROL UNIT THAT RELATE TO PENDING DRUG APPLICATIONS; FAILURE TO FOLLOW WRITTEN PROCEDURES RELATED TO (b) (4) AND, LACK OF A VALIDATED CLEANING PROCESS FOR AN INJECTABLE PRODUCT.</p> <p>PREVIOUS INSPECTIONS OF THE FACILITY CONDUCTED (b) (4) WERE CLASSIFIED NAI AND VAI, RESPECTIVELY. THE 2008 ESTABLISHMENT INSPECTION RESULTED IN CITATIONS RELATED TO ISSUES INCLUDING, BUT NOT LIMITED TO: REPROCESSING MATERIALS WITHOUT PERFORMING INVESTIGATIONS; FAILURE TO VALIDATE CLEANING PROCESSES; FAILURE OF THE QUALITY CONTROL UNIT TO PERFORM ACTIVITIES RELATED TO CLINICAL TRIAL MATERIALS; FAILURE OF THE QUALITY CONTROL UNIT TO REVIEW SIGNIFICANT CHANGES; FAILURE OF THE EQUALITY CONTROL UNIT TO REVIEW AND APPROVE INVESTIGATIONS AND CORRECTIVE ACTIONS.</p> <p>THE ATLANTA DISTRICT IS RECOMMENDING THAT THIS FACILITY BE APPROVED TO PERFORM THE ACTIVITIES ASSIGNED TO IT IN THIS APPLICATION.</p>					
OC RECOMMENDATION	05-OCT-2012			ACCEPTABLE	SMITHDE DISTRICT RECOMMENDATION

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

SUBMITTED TO OC	03-JUN-2011		HENRYD
SUBMITTED TO DO	08-JUN-2011	<b>Product Specific</b>	INYARDA
REVIEWER WOULD LIKE TO PARTICIPATE ON INSPECTION			
ASSIGNED INSPECTION TO IB	05-JUL-2011	<b>Product Specific</b>	JCHANCEY
INSPECTION SCHEDULED	05-JUL-2011	15-JUL-2011	JCHANCEY
REQUEST CANCELLED	21-JUL-2011		BOUIET
		REFUSE TO FILE	
SUBMITTED TO OC	04-JAN-2012		HEIMANNM
SUBMITTED TO DO	06-JAN-2012	10-Day Letter	INYARDA
NME BUT ACCEPTABLE FOR PACKAGING?			
DO RECOMMENDATION	17-JAN-2012	ACCEPTABLE	JCHANCEY
THE MOST RECENT INSPECTION OF THIS FACILITY WAS CONDUCTED IN THE ISSUANCE OF AN 8-POINT FDA-483 CITING THE FIRM FOR:			
		(b) (4) RESULTED	BASED ON FILE REVIEW
<ul style="list-style-type: none"> <li>- INADEQUATE (b) (4) PROCEDURES</li> <li>- INADEQUATE INVESTIGATIONS INTO PROCESS DEVIATIONS</li> <li>- FAILURE TO INVESTIGATE ALL PROCESS DEVIATIONS</li> <li>- INADEQUATE STABILITY PROTOCOLS</li> <li>- INADEQUATE (b) (4) INTEGRITY TESTING PROCEDURES</li> <li>- SUBMITTING REGULATORY FILINGS PRIOR TO ESTABLISHING WRITTEN PROCEDURES AND ANALYTICAL METHODS</li> <li>- FAILURE TO FOLLOW SOPS RELATED TO TRAINING, IMPLEMENTATION OF CORRECTIVE AND PREVENTATIVE ACTIONS, AND QA ACTIVITIES</li> <li>- FAILURE TO VALIDATE CLEANING PROCEDURES</li> <li>- FAILURE TO ASSESS ALL POTENTIAL PRODUCT-CONTACT SURFACES DURING CLEANING VALIDATION</li> </ul>			
PREVIOUS INSPECTIONS OF THE FACILITY CONDUCTED (b) (4) WERE CLASSIFIED NAI AND VAI, RESPECTIVELY. THE 2008 INSPECTION RESULTED IN A 13-POINT FDA-483 THAT INCLUDED CITATIONS FOR:			
<ul style="list-style-type: none"> <li>- FAILURE TO INITIATE DEVIATIONS</li> <li>- FAILURE TO VALIDATE CLEANING PROCEDURES</li> <li>- FAILURE TO EVALUATE THE IMPACT OF INTRODUCING CLINICAL TRIAL MATERIALS TO PRODUCTION EQUIPMENT</li> <li>- FAILURE TO APPROVE A DEVIATION AND MULTIPLE CHANGE CONTROLS PRIOR TO INITIATING THEM</li> <li>- FAILURE TO FOLLOW CLEANING VALIDATION SOPS</li> <li>- FAILURE TO EXPAND INVESTIGATIONS TO INCLUDE ALL POTENTIALLY AFFECTED PRODUCTS</li> <li>- FAILURE TO CONSISTENTLY COMPLETE CAPAS BY THEIR DUE DATES</li> </ul>			
THE ATLANTA DISTRICT IS RECOMMENDING THAT THIS FACILITY BE APPROVED TO PERFORM THE ACTIVITIES DESCRIBED IN THIS APPLICATION.			
OC RECOMMENDATION	17-JAN-2012	ACCEPTABLE	SMITHDE
		DISTRICT RECOMMENDATION	

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/s/  
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MARY GRACE LUBAO  
11/26/2012

ONDQA Division Director's Memo  
NDA 202834, FYCOMPA (perampanel) Tablets  
2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg  
Date: 10-OCT-2012

## **Introduction**

FYCOMPA (perampanel) Tablets are immediate release tablets which are manufactured in six different dosage strengths: 2, 4, 6, 8, 10, and 12 mg. The recommended initial daily dose of FYCOMPA is 2 mg. The proposed indication is treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy, aged 12 years and older.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation was issued by the Office of Compliance on 10-OCT-2012.

***ONDQA recommends approval of this NDA. There are no pending deficiencies from a CMC standpoint.***

## **Administrative**

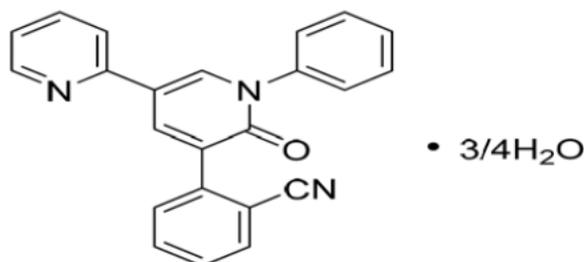
The original submission of this 505(b)(1) NDA was received 22-DEC-2011 from Eisai, Inc. Four (4) CMC amendments were also reviewed during the review cycle. All Chemistry, Manufacturing and Controls assessment is captured in the following reviews, respectively: Chemistry Review #1 (15-AUG-2012, Dr. L. Soldatova), the follow-up Chemistry Memorandum (28-SEP-2012, Dr. L. Soldatova) and the ONDQA Biopharmaceutics Review #1 (22-AUG-2012, Dr. T. Chen).

The NDA is supported by IND 68,368 and six (6) drug master files (DMFs). An overall "acceptable" recommendation was issued in EES (10-OCT-2012), and acceptable container/carton labeling was received on 02-JUL-2012.

***This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint. Confirmatory language regarding the expiration dating periods is not needed as the Agency concurs with the expiration dating periods proposed in the Applicant's NDA submission.***

## Drug Substance (perampanel)

Chemical Name: 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate (4:3)] (MW=362.9 g/mol, C<sub>23</sub>H<sub>15</sub>N<sub>3</sub>O/4H<sub>2</sub>O)



Perampanel is a first-in-class, selective, noncompetitive antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Perampanel is a white to yellowish white powder at room temperature; it is not hygroscopic, (b) (4). Perampanel exists in different polymorphic or pseudopolymorphic forms, including five anhydrous forms and one hydrate; the drug substance perampanel is controlled as 3/4 hydrate. Perampanel is (b) (4) practically insoluble in water and heptane, (b) (4).

Perampanel is manufactured via conventional synthetic methodology, and the proposed starting materials were discussed and confirmed with the Agency prior to the NDA submission.

Perampanel is relatively stable, and no extraordinary storage precautions are required other than standard protection. The proposed **re-test period** of (b) (4) when stored in the recommended container closure system at ambient storage conditions was confirmed as acceptable in the CMC review.

## Drug Product, FYCOMPA (perampanel) Tablets

FYCOMPA Tablets are film-

The manufacturing

Perampanel tablets will be packaged in 30- and 90-count 50 cc HDPE bottles with a child-resistant closure; a physician sample, (b) (4)/aluminum blister will contain 7 x 2 mg tablets and 7 x 4 mg tablets (Starter Kit). The adequacy of all proposed packaging materials for their intended use was confirmed as part of the CMC review (see Chemistry Review #1).

According to the 15-AUG-2012 Chemistry Review, the Applicant's primary stability data package adequately supports the proposed expiration dating periods. Therefore, there is no need for confirmatory language regarding the expiration dating period in the action letter.

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/s/  
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SARAH P MIKSINSKI  
10/11/2012

## Memorandum of Recommendation

NDA # 202-834  
Date: 28 August 2012  
Product Name: Fycompa (perampanel) Tablets, 2, 4, 6, 8, 10, 12 mg  
Company Name: Eisai, Inc.  
Subject: Amendment 08/20/2012  
Reviewer: Lyudmila Soldatova, Ph.D.

### **BACKGROUND**

#### Agency's Recommendation for Eisai during the Teleconference held on 08/09/2012

The Agency requested that the applicant replace the Master Lot packaging record for Banzel 400mg (Rufinamide) Tablets in 120 cc bottles, which is not relevant to Perampanel, tablets, with the executed packaging batch record for Perampanel tablets used for stability studies that are packaged in the bottles and blisters (representative batch record).

The Agency clarified that 1 example of bottle executed packaging batch records and 1 example of blister executed packaging batch records for drug product batches used for stability studies will be sufficient. The applicant stated that current batch records are in Japanese and that it would take at least 2 weeks for the information to be translated. Agency requested that the applicant submits the batch records in a separate amendment when the translated version becomes available; and Eisai agreed to provide the translated batch record within 2 weeks (refer to the Meeting Minutes dated 09-Aug-2012).

#### The Eisai Response (Amendment 08/20/2012)

The applicant has provided the Executed Packaging Batch Records (Stability Study) for 4 mg tablets packaged in 50 cc HDPE bottles (30 counts), and Executed Packaging Batch Records (Stability Study) for 4 mg tablets packaged in (b) (4) blisters.

**EVALUATION:** The representative Executed Packaging Batch Records for 4 mg tablets packaged in HDPE bottles and in blisters, provided by Eisai, are acceptable.

### **Recommendation and Conclusion on Approvability**

NDA 202-834 for Fycompa (perampanel) Film-coated Tablets, 2 mg, 4 mg, 6 mg, 8 mg, and 12 mg, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint with pending OC recommendation for drug substance and drug product facilities.

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/s/  
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LYUDMILA SOLDATOVA  
08/28/2012

RAMESH K SOOD  
08/28/2012

**NDA 202-834**

**Perampanel Tablet**

**Eisai, Inc.**

**Lyudmila N. Soldatova, Ph.D.**  
**Office of New Drug Quality Assessment**  
**for**  
**Division of Neurology Drug Products**

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# Chemistry Review Data Sheet

1. NDA 202-834
2. REVIEW: #1
3. REVIEW DATE: August 15, 2012
4. REVIEWER: Lyudmila N. Soldatova, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 68,368

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedOriginal  
Amendment  
Amendment  
AmendmentDocument Date22-DEC-2011  
11-APR-2012  
02-JUL-2012  
15-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Eisai Inc.  
Address: 100 Tice Boulevard  
Woodcliff Lake, NJ 07667  
Representative: Heather A. Bradley, MPH, Senior Manager,  
Regulatory Affairs  
Telephone: 201-949-4691

8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: FYCOMPA  
b) Non-Proprietary Name (USAN): Perampanel  
c) Code Name/# (ONDC only): E2007  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Epilepsy: Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

**Chemical Name:**

2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate (4:3) [IUPAC]

Benzonitrile, 2-(1',6'-dihydro-6'-oxo-1'-phenyl[2,3'-bipyridin]-5'-yl)- [CAS]

Perampanel [USAN, INN]

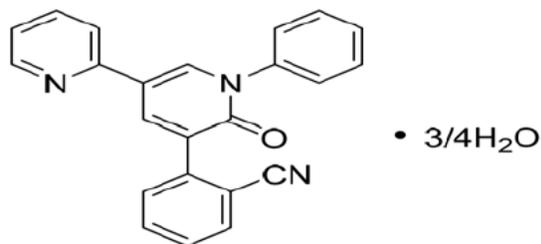
**Molecular Formula:**

C<sub>23</sub>H<sub>15</sub>N<sub>3</sub>O • 3/4H<sub>2</sub>O

**Relative Molecular Mass:**

362.90 (3/4 hydrate)

(b) (4)



**CAS Registry No.**

380917-97-5

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4	N/A	N/A	(b) (4)
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	

<sup>1</sup> 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")

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

**B. Other Documents:**

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 68,368		

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending		
Biopharm/ONDQA	Pending		
DMEPA	Pending		
Methods Validation	Pending: Method Validation Request for Assay and Related Substances (Drug Product) <sup>(b) (4)</sup> and <sup>(b) (4)</sup> (Drug Substance)	Requested 09-Feb-2012 and 27-Apr-2012, respectively	Division of Pharmaceutical Analysis, St. Louis, MO
EA	Categorical exclusion is granted as per this Review	09-May-2012	Lyudmila N. Soldatova, PhD

# The Chemistry Review for NDA 202-834

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 202-834 for Fycompa (perampanel) Film-coated Tablets, 2 mg, 4 mg, 6 mg, 8 mg, and 12 mg, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint with pending OC recommendation for drug substance and drug product facilities, and with pending submission of the translated executed packaging batch records. The NDA deficiencies have been resolved. Based on the drug product stability data, the following expiration dating period is recommended:

- 48 months for Fycompa (perampanel) Film-coated Tablets, 2 mg and 4 mg, (b) (4) and in HDPE bottles (30 tablets and 90 tablets)
- 24 months for Fycompa (perampanel) Film-coated Tablets, 6 mg, 8 mg, 10 mg, and 12 mg (b) (4) and in HDPE bottles (30 tablets and 90 tablets)
- 48 months for Starter Kit blister containing 7 counts of 2 mg tablets and 7 counts of 4 mg tablets

Since the assigned expiration dating periods are the same as requested by Eisai, they do not have to be included in the Action Letter.

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

None as per this review.

### II. Summary of Chemistry Assessments

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

The perampanel film-coated tablets are immediate release tablets that are manufactured in six different strengths: 2, 4, 6, 8, 10, and 12 mg perampanel. The tablet strengths represent the amount of the perampanel (b) (4), and quantity of the drug substance perampanel in the tablet formulation is (b) (4)

The perampanel 2, 4, 6, 8, 10, and 12 mg film-coated tablets are round, biconvex film-coated tablets, distinguished by color and debossing; 2 mg tablets are 105 mg in weight and 6.6 mm in diameter, and the 4, 6, 8, 10, and 12 mg tablets are 210 mg in weight and 8.1 mm in diameter. The colors of perampanel 2, 4, 6, 8, 10, and 12 mg film-coated tablets are orange, red, pink, purple, green, and blue, respectively. The compositions of the (b) (4) of (b) (4)

## Executive Summary Section

(b) (4) (b) (4)  
(b) (4)  
All excipients in perampanel tablets are common excipients that are used in solid oral dosage forms; they are compendial, of USP/NF/Ph.Eur quality. The non-compendial (b) (4) are used to provide distinctive colors for different dosage strengths. The manufacture (b) (4)

The Critical Process Parameters (CPPs) and the Critical Quality Attributes (CQAs) that may impact the efficacy or safety of the drug product were evaluated during manufacturing development, and the established Proposed Operating Conditions have been identified and implemented in the manufacture of commercial scale drug product batches. The perampanel tablets are manufactured by Eisai at the Kawashima plant in Kakamigahara-shi, Japan. Standard specifications for solid oral dosage forms have been proposed; dissolution method was evaluated by ONDQA biopharmaceutics reviewer. The firm accepted revision of the dissolution acceptance criterion from Q = (b) (4) dissolved in (b) (4) to Q (b) (4) in 15 minutes as requested by ONDQA biopharmaceutics reviewer. Perampanel tablets will be packaged in 30- and 90-count 50 cc HDPE bottles with a child-resistant closure; a physician sample, (b) (4)/aluminum blister will contain 7 x 2 mg tablets and 7 x 4 mg tablets (Starter Kit). On request, Eisai will provide the translated executed packaging batch records in a separate Amendment (refer to the Section R1 of this Review). The NDA stability package includes the 48-months long term data (30°C/65% RH) and 6-month accelerated data (40°C/75% RH) for three lots per strength for 2 mg and 4 mg tablets, packaged in 30- and 90-count HDPE bottles. For higher strengths tablets, the 12-months long term data and 6-month accelerated data are provided for three lots each of the 6 mg and 12 mg tablets, and for one lot each of 8 mg and 10 mg. The stability protocol utilizes a reduced testing, i.e., matrixing and bracketing design for all packaging configurations. The requested shelf life of 48 months for perampanel 2 mg and 4 mg tablets (b) (4) in HDPE bottles (30 count and 90 count), and the requested shelf life of 24 months for 6, 8, 10 and 12 mg tablets (b) (4) and in HDPE bottles (30 count and 90 count) could be potentially granted based on the stability data. The proposed storage conditions are: Store at 25°C (77°F). Excursions permitted 15-30°C (59-86°F).

The active ingredient, perampanel [chemical name 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzotrile hydrate (4:3)] is a small molecule with molecular formula C<sub>23</sub>H<sub>15</sub>N<sub>3</sub>O•3/4H<sub>2</sub>O and molecular weight 362.90. Perampanel is a first-in-class, selective, non-competitive antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Perampanel is white to yellowish white powder; it is not hygroscopic, (b) (4). Perampanel exists in different polymorphic or pseudopolymorphic forms, including five anhydrous forms and one hydrate; the drug substance perampanel is controlled as 3/4 hydrate. Perampanel is (b) (4) (b) (4) practically insoluble in water and heptane, (b) (4) (b) (4). The perampanel drug substance is manufactured (b) (4)

## Executive Summary Section

(b) (4)

according to the preliminary agreement with the Agency. The necessary information is provided for two starting materials: the synthetic scheme and short description of the synthesis, specifications and their justification, analytical procedures and their validation, and batch analysis. The bulk drug substance is manufactured by Eisai at the firm's Kashima plant in Ibaraki-ken, Japan. The specification of perampanel includes test parameters that are typical for small molecule.

(b) (4)

The two potentially genotoxic impurities, (b) (4) are controlled by the total amount of (b) (4) with the limit of NMT (b) (4) in this specification.

A categorical exclusion from the preparation of an environmental assessment is claimed by the firm, as provided under 21 CFR 25.31(b).

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

The subject of the NDA is Fycompa™ (perampanel) Tablets, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg, being developed by Eisai, Inc. for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

#### Proposed Fycompa Administration

FYCOMPA should be taken once daily before bedtime.

- Partial-onset Seizures: Treatment with FYCOMPA should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by 2 mg/day increments to a dose of 4 mg to 12 mg/day. The maximum recommended daily dose is 12 mg. Dose increases should occur no more frequently than at weekly intervals.

### C. Basis for Approvability or Not-Approval Recommendation

NDA 202-834 is recommended for APPROVAL from CMC standpoint with pending overall OC recommendation, and with pending submission of the translated executed packaging batch records. The NDA deficiencies have been resolved in the firm's response to issues raised in the IR Letter dated 07-Jun-2012, and through the teleconference on 09-Aug-2012. The results of Method Validation Consult for (b) (4) for residual elements (b) (4) is pending but validation of the analytical methods was found acceptable by this reviewer.

## III. Administrative

### A. Reviewer's Signature

*Lyudmila Soldatova*

### B. Endorsement Block

ChemistName: Lyudmila N. Soldatova, Ph.D.

Chemistry Branch Chief: Ramesh K. Sood, Ph.D.

Chemistry Project Manager Name: Teshara Bouie

## Executive Summary Section

- C. CC Block**  
See DARRTS.

109 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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LYUDMILA SOLDATOVA  
08/16/2012

RAMESH K SOOD  
08/16/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration

---

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3897

Date: July 10, 2012  
To: Lyudmila Soldatova CMC Reviewer  
Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)  
From: Wei Ye, Chemist (HFD-920)  
Subject: Method Validation for NDA 202834  
Fycompa (Perampanel Tablets), 2 mg and 12 mg  
Eisai Inc.

The following method was evaluated and is acceptable for quality control and regulatory purposes:

- Assay and Related Substances  
(Eisai Inc., Method 3.2.P.5.2.4, page 2)

## Summary of Results

NDA 202834

- Assay and Related Substances  
(Eisai Inc., Method 3.2.P.5.2.4, page 2)

### Assay

Strength	Sample1	Sample2	Avg.(2)	Limit	Pass/Fail
2 mg	101.2	102.2	101.7	(b) (4)	Pass
12 mg	103.6	102.8	103.2	(b) (4)	Pass

### Related Substances

Strength	Sample	Limit		Pass/Fail
2 mg	ND	Individual NMT (b) (4)	; Total NMT (b) (4)	Pass
12 mg	ND	Individual NMT (b) (4)	; Total NMT (b) (4)	Pass

Note:

- Only more than (b) (4) individual related substance is reported
- ND – not detected

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/s/  
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MICHAEL L TREHY  
07/17/2012

BENJAMIN J WESTENBERGER  
07/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Benjamin (Nick) Westenberger**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** Lyudmila Soldatova, CMC Reviewer  
Martha Heimann, CMC Lead  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: lyudmila.soldatova@fda.hhs.gov  
Phone: (301)-796-1758  
Fax.: (301)-796-9747

**Through:** Ramesh Sood, Branch Chief  
Phone: (301)-796-1466

**and**

Michael Folkendt, Associate Director for Regulatory Affairs  
Phone: 301-796-1670

**SUBJECT:** Methods Validation Request

---

Application Number: NDA 202834

Name of Product: Fycompa (perampanel tablets), 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

Applicant: Eisai, Inc.

Applicant's Contact Person: Heather A Bradley, MPH, Senior Manager, Regulatory Affairs

Address: 100 Tice Boulevard, Woodcliff Lake, NJ 07667

Telephone: 201-949-4691

Fax: 201-949-4915

---

Date NDA Received by CDER: **22-Dec-2011** (resub. After RTF) Submission Classification/Chemical Class: 1S (NME)

Date of Amendment(s) containing the MVP: **25-May-2011** Special Handling Required: No

DATE of Request: **24-April-2012**

DEA Class: N/A

Requested Completion Date: **22-Jul-2012**

**Format of Methods Validation Package (MVP)**

PDUFA User Fee Goal Date: **22-Oct-2012**

Paper  **Electronic**  Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

---

MVP Reference #	<b>METHODS VALIDATION REQUEST</b>			NDA # 202834
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Perampanel – reference standard	To be determined by lab	Lot 15012059		
Perampanel Drug Substance	To be determined by lab	Lot 10671803		
(b) (4)	To be determined by lab	(b) (4)		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1 and 4.2
Supporting Data for Accuracy, Specificity, etc.				3.2.P.S.4.3; See also Item 3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.4.4
Other:				N/A
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
Drug Substance	Residual elements (b) (4) by (b) (4)	3..2.S.4.2.8	0	The (b) (4) potential mutagens are controlled by the content of (b) (4) Method Validation Report in 3.2.S.4.3
Additional Comments:				

**Methods Validation Request Criteria**

<b>MV Request Category</b>	<b>Description</b>
<b>0</b>	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
<b>1</b>	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
<b>2</b>	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
<b>3</b>	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
<b>4</b>	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
<b>5</b>	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
<b>6</b>	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
<b>7</b>	Methods that are subject to a “for cause” reason

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/s/  
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LYUDMILA SOLDATOVA  
04/27/2012

RAMESH K SOOD  
04/27/2012

MICHAEL M FOLKENDT  
04/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Benjamin (Nick) Westenberger**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** Lyudmila Soldatova, CMC Reviewer  
Martha Heimann, CMC Lead  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: lyudmila.soldatova@fda.hhs.gov  
Phone: (301)-796-1758  
Fax.: (301)-796-9747

**Through:** Ramesh Sood, Branch Chief  
Phone: (301)-796-1466

**and**

Jeannie David, ONDQA Methods Validation Project Manager  
Phone: 301-796-4247

**SUBJECT:** Methods Validation Request

---

Application Number: NDA 202834

Name of Product: Fycompa (perampanel tablets), 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

Applicant: Eisai, Inc.

Applicant's Contact Person: Heather A Bradley, MPH, Senior Manager, Regulatory Affairs

Address: 100 Tice Boulevard, Woodcliff Lake, NJ 07667

Telephone: 201-949-4691

Fax: 201-949-4915

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Date NDA Received by CDER: **22-Dec-2011** (resub. After RTF) Submission Classification/Chemical Class: 1S (NME)

Date of Amendment(s) containing the MVP: **25-May-2011**

Special Handling Required: No

DATE of Request: **02-Feb-2012**

DEA Class: N/A

Requested Completion Date: **22-Jul-2012**

**Format of Methods Validation Package (MVP)**

PDUFA User Fee Goal Date: **22-Oct-2012**

Paper  **Electronic**  Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

---

MVP Reference #	<b>METHODS VALIDATION REQUEST</b>			NDA # 202834
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Perampanel – reference standard	To be determined by lab	15012059		
(b) (4)	To be determined by lab	14052455		
Perampanel 2 mg tablet, 90-ct bottle	To be determined by lab	07060601		
Perampanel 12 mg tablet, 90-ct bottle	To be determined by lab	01012701		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1 and 4.2
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1 and 5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.P.S.4.3 / 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.4.4 / 3.2.P.5.4
Other:				N/A
⇒ ITEM 3: REQUESTED DETERMINATIONS				
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
	Assay and Related Substances (Tablet)	3..2.P.5.2.3	0	(b) (4) Please do determination on both strengths
Additional Comments:				

## Methods Validation Request Criteria

MV Request Category	Description
<b>0</b>	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
<b>1</b>	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
<b>2</b>	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
<b>3</b>	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
<b>4</b>	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
<b>5</b>	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
<b>6</b>	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
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/s/  
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MARTHA R HEIMANN  
02/02/2012

RAMESH K SOOD  
02/02/2012

JEANNIE C DAVID  
02/09/2012  
ONDQA Methods Validation Project Manager

Initial Quality Assessment  
Branch I  
Division of New Drug Quality Assessment I

**OND Division:** Division of Neurology Products  
**NDA:** 202-834  
**Applicant:** Eisai, Inc.  
**Stamp Date:** 25-May-2011  
**PDUFA Date:** 25-Mar-2012  
**Trademark:** Fycompa is proposed  
**Established Name:** Perampanel  
**Dosage Form:** Tablet  
**Route of Administration:** Oral  
**Indication:** Epilepsy  
  
**CMC Lead:** Martha R. Heimann, Ph.D.

	Yes	No
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## Summary and Critical Issues:

### Summary

Perampanel (codename E2007) is a first-in-class, selective, non-competitive antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. It is thought that activation of AMPA receptors by glutamate is responsible for most fast excitatory synaptic transmission in the brain. In *in-vitro* studies, perampanel inhibited AMPA-induced increase in intracellular calcium.

Perampanel was identified and developed by Eisai, Inc. It has been investigated for multiple indications including treatment of neuropathic pain, migraine prophylaxis, epilepsy, and Parkinson's disease. Development for the epilepsy indication was performed under IND 68,368.

The current NDA provides for an immediate release perampanel tablet formulation to be available in six strengths, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg. The product is intended for use in the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. The recommended target doses are between 4 mg/day and 12 mg/day. The product should be taken once daily before bedtime.

Prior to submission of the NDA, the applicant sought written advice on three occasions. There were no CMC related meetings.

In the 18-Oct-2006 submission to IND 68,368, the applicant requested Agency agreement on designation of [REDACTED] (b) (4)

[REDACTED] The Agency agreed to this proposal; however, the firm was advised (via e-mail dated 30-Jan-2007) to include information [REDACTED] (b) (4) [REDACTED] (b) (4) in the NDA.

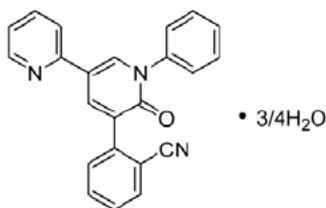
The requested information for (b) (4) and corresponding information on the synthesis of (b) (4) are provided in the submission.

(b) (4) Subsequently, a special protocol assessment for reduced stability testing of the 6 mg, 8 mg, 10 mg and 12 mg tablets was submitted on 28-Oct-2009. Per Agency correspondence dated 02-Dec-2009, there was no agreement; however the Agency provided advice. The stability package submitted in the NDA is consistent with the advice provided to the sponsor.

### Drug Substance

The active ingredient, perampanel [chemical name: 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzotrile hydrate (4:3)], is a well characterized small molecule with molecular formula  $C_{23}H_{15}N_3O \cdot 3/4H_2O$  and molecular weight (b) (4) or 362.90 (3/4 hydrate). Perampanel is (b) (4) practically insoluble in water (b) (4)

(b) (4) The drug substance is non hygroscopic. Four anhydrous polymorphic forms and one hydrate are described in the application. The bulk drug substance is controlled as the 3/4 hydrate. The chemical structure of perampanel is:



The bulk drug substance is manufactured by Eisai at the firm's Kashima plant in Ibaraki-ken, Japan. The synthetic routes for the designated starting materials (b) (4) Detailed process information is not provided.

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immediately following this page

The proposed drug substance specification is given in applicant's **Table 3.2.S.4.1-1**, which is reproduced below. The specification for perampanel includes test parameters that are typical for a small molecule. Assay and Related Substances are determined by a reverse phase gradient HPLC method using a water, acetonitrile and ammonium acetate mobile phase and UV detection at 290 nm. There are a number of specified impurities with limits set at or below the ICH qualification threshold. Note that the specification includes a test for (b) (4)

(b) (4) in the manufacture of (b) (4)

**Table 3.2.S.4.1-1 Specifications for Perampanel**

Test Item	Acceptance Criteria	Test Method (Section)
Description (Appearance)	White to yellowish white powder	Visual inspection (3.2.S.4.2.1)
Identification (IR)	Conforms to standard	IR spectroscopy (3.2.S.4.2.2)
X-ray powder diffraction	Conforms to standard	X-ray powder diffraction (3.2.S.4.2.3)
Heavy metals	(b) (4)	USP <231> (3.2.S.4.2.4)
Related substances (HPLC)	(b) (4)	Gradient HPLC (3.2.S.4.2.5)
Residual solvents (1)	(b) (4)	GC (3.2.S.4.2.6)
Residual solvents (2)	(b) (4)	GC (3.2.S.4.2.7)
Residual elements	(b) (4)	(b) (4)
Residue on ignition	(b) (4)	Harmonized method (JP/USP/Ph.Eur.) (3.2.S.4.2.9)
Water content	(b) (4)	Coulometric Karl Fischer titration (3.2.S.4.2.10)
Particle size	(b) (4)	Light diffraction measurement USP <429> (3.2.S.4.2.11)
Assay (HPLC)	(b) (4)	Gradient HPLC (3.2.S.4.2.5)
Microbial limits Microbial enumeration tests Total aerobic microbial count Total combined yeasts/moulds count Test for specified micro-organisms: <i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i>	(b) (4)	Microbial limit tests (3.2.S.4.2.12)

The drug substance primary stability package includes 60 months of long-term/intermediate stability data (30°C/65% R. H.) and six months of accelerated data (40°C/75% R. H.) for three pilot scale batches of drug substance manufactured at the commercial site. A (b) (4) retest date is proposed.

Drug Product

The proposed dosage form is an immediate tablet containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg perampanel. The components and composition of Perampanel Tablets are summarized in the applicant's **Table 3.2.P.1-2** which is shown below.

**Table 3.2.P.1-2 Components and Composition of Perampanel Film-coated Tablets**

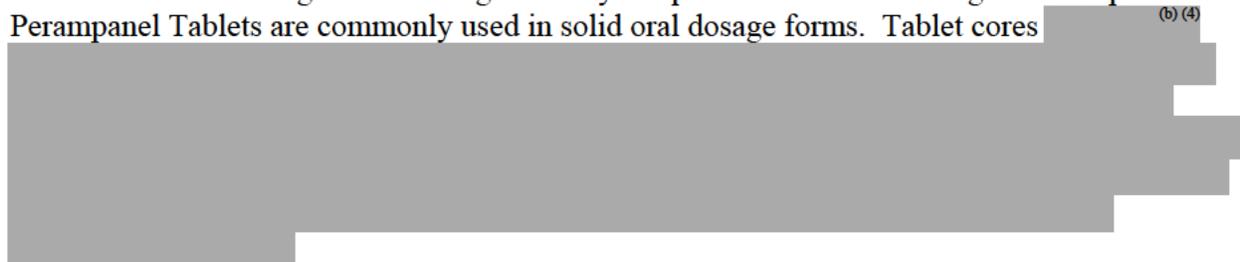
Ingredient	Dosage Strength of Perampanel Film-coated Tablets						Function	Specification
	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg		
(b) (4)	Amount (mg)						(b) (4)	
(b) (4)							Active Ingredient (b) (4)	In-house (E2007)
								NF
								NF
								USP
								USP
								NF
								NF
								NF
								-
								In-house (03F43101)
								In-house (03F45059)
								In-house (03F44071)
In-house (03F40008)								
In-house (03F41127)								
In-house (03F40557)								
USP								
Total Weight (mg)	105	210	210	210	210	210	-	-

NF = National Formulary (U.S.), q.s. = quantum sufficit. USP = United States Pharmacopeia.

(b) (4)



Perampanel Tablets are round, biconvex, film-coated tablets. The 2 mg tablet is 105 mg in weight and 6.6 mm in diameter. The remaining strengths are 210 mg in weight and 8.1 mm in diameter. Tablet strengths are distinguished by unique colors and debossing. All excipients in Perampanel Tablets are commonly used in solid oral dosage forms. Tablet cores (b) (4)



The proposed commercial formulations for 2 mg and 4 mg Perampanel Tablets (Formulation C) are the same, except for debossed code, as for the products used in pivotal clinical studies. The applicant cites BE study E2007-E044-016 (4 mg tablet vs. 2 x 2 mg tablets) to support the BE of these strengths. Comparative dissolution data are also provided.

The 6 mg, 8 mg, 10 mg and 12 mg tablet formulations (Formulation D) were developed to cover marketing requirements for higher doses and were not used in clinical trials other than BE. The applicant appears to have conducted three BE studies comparing formulation D to Formulation C. Studies E2007-E044-037 and E2007-E044-040 compared the bioavailability of one 12 mg Perampanel Tablets to that of six 2 mg Perampanel Tablets. Study E2007-E044-039 compared one 6 mg tablet to three 2 mg tablets.

Perampanel Tablets are manufactured by Eisai at the Kawashima plant in Kakamigahara-shi, Japan. (b) (4)



The proposed specification for Perampanel Tablets, 2 mg is given in the applicant's **Table 3.2.P.5.1-1**, which is shown below. With the exception of appearance, specifications for the higher strengths are the same.

**Table 3.2.P.5.1-1 Specification for Perampanel 2 mg Film-coated Tablets**

Test Item	Acceptance Criteria	Analytical Procedure / Section
Description	Orange, round, biconvex, film-coated tablet, debossed, "C275" on one side, and "2" on the other.	Visual inspection /3.2.P.5.2.1
Identification by retention time	Conforms to the retention time of standard peak	HPLC /3.2.P.5.2.2
Identification by UV spectrum <sup>a</sup>	Conforms to the standard UV spectrum	PDA or UV /3.2.P.5.2.3
Assay	95.0% – 105.0% of the stated content	HPLC /3.2.P.5.2.4
Related substances Individual Total	Not more than (b) (4) Not more than (b) (4)	HPLC /3.2.P.5.2.4
Dissolution	Not less than (b) (4) (Q) in (b) (4) Per Acceptance Table 1, USP <711> or Table 2.9.3-1, Ph. Eur. 2.9.3.	USP <711> or Ph. Eur. 2.9.3. Apparatus 2 /3.2.P.5.2.5
Content Uniformity* (Uniformity of Dosage Units)	Meets the requirements of USP <905> or Ph. Eur. 2.9.40.	USP <905> or Ph. Eur. 2.9.40. HPLC /3.2.P.5.2.6
Microbial limits: <sup>b</sup> Microbial enumeration tests: Total aerobic microbial count Total combined yeasts/moulds count Test for specified micro-organisms: <i>Escherichia coli</i> . <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i>	Not more than 10 <sup>3</sup> CFU/g Not more than 10 <sup>2</sup> CFU/g  Absence in 1g Absence in 1g Absence in 1g	Harmonized method of USP<61> and <62> or Ph. Eur. 2.6.12., 2.6.13. /3.2.P.5.2.7

a: The UV spectrum for identification can be obtained by HPLC (PDA) or UV spectrophotometer.

b: Microbial limit tests are not routinely tested at release (if the test results for the first three production batches meet the specification, microbial limit tests will be performed on one batch per year thereafter).

\*Not a stability parameter

Analytical procedures are straightforward. Assay and Related Substances are determined using the same gradient reverse phase HPLC method as used for the bulk drug substance. Content Uniformity is determined using a related isocratic HPLC method. Dissolution is determined using USP Apparatus 2 with 0.1 N HCl as the medium and paddle speed 50 rpm. Dissolution is quantitated by UV.

Perampanel Tablets will be packaged in 30- and 90-count 50 cc HDPE bottles with child-resistant closures and in (b) (4)/aluminum blisters.

Due to the number of tablets strengths and the (b) (4) the NDA stability package is somewhat complex. All stability lots except one (Lot P5X003ZZ, 4 mg) were manufactured at the proposed commercial scale at the Kawashima plant. Lot P5X003ZZ was manufactured at (b) (4) at the (b) (4) at

the Kawashima Site. All lots were placed on stability in 30- and 90-count bottles and (b) (4)/aluminum blisters.

For 2 mg and 4 mg tablets, the applicant provides 48 months of long term data (30°C/65% R. H.) and 6 months accelerated data for three lots of per strength packaged in 30- and 90-count HDPE bottles and blisters. The stability protocol incorporates a reduced testing matrix for all packaging configurations. The stability matrix provides for a one half reduction in testing at the 3, 6, 9 and 18 month long-term and 1 and 3 month accelerated time points, with full testing at the remaining time points.

For the higher strengths the stability package includes data through 6 months at 30°C/65% R. H. for 3 three lots each of the 6 mg and 12 mg tablets and one lot each for 8 mg and 10 mg tablets. As for the lower strengths, a reduced testing matrix is used. For the higher strengths, however; the protocol includes full testing of all lots at the 6 month time, which is the last time point submitted in the original NDA. The protocol also provides for full testing of the 8 mg and 10 mg tablets.

The applicant proposes a 48 month expiration dating period for 2 mg and 4 mg tablets, which is consistent with the extent of data provided in the NDA. For 6 mg, 8 mg, 10 mg and 12 mg tablets a 24 month expiration dating period is proposed; however, only 6 months data are provided. It is noted that the applicant intends to submit 12 month data during the review cycle. The firm was advised, in correspondence dated 01-Dec-2009, that additional data received prior to mid cycle would be reviewed as part of the original application.

### ***Critical issues for review***

The designated starting materials for perampanel. (b) (4) (b) (4)  
(b) (4) (b) (4)  
Therefore controls on the starting materials are considered critical for product quality.

No critical issues related to the drug product were identified in the initial assessment.

### ***Additional issues***

*Administrative:* The firm has submitted a claim for categorical exclusion under 21 CFR 25.31(b) which states that the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below one part per billion (1 ppb).

*Establishment Evaluation:* A full list of facilities involved in the manufacture, packaging and testing of perampanel and Perampanel Tablets is provided in the submission. Facilities requiring compliance evaluation were entered into EES on 03-Jun-2011.

*Labeling/Established Name:* The active ingredient, perampanel, is the free base. Therefore there are no issues of consistency between the established name “perampanel tablets” and the label potency. The draft labeling provided in the application includes bottle labels and blister labeling

for a 2 mg/4 mg professional sample “starter pack.” [REDACTED] (b) (4)

### **Comments for 74-Day Letter**

The following comment may be communicated as an information request.

Your application includes container labels for 30- and 90-count bottles and a 2 mg/4 mg professional sample “starter pack.” [REDACTED] (b) (4)

### **Review, Comments and Recommendation:**

The NDA is fileable from a CMC perspective.

The drug substance is a well-characterized small molecule and the drug product is a simple immediate release tablet. There are no QbD aspects to the submission. It is recommended that the review team include a single CMC reviewer and a Biopharmaceutics reviewer. The drug substance is a new molecular entity; therefore, a Division-level regulatory briefing would be appropriate.

*{See appended electronic signature page}*

Martha R. Heimann, Ph.D.  
CMC Lead, DNDQA-1, ONDQA

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief, DNDQA-1, ONDQA

**ATTACHMENT 1****Manufacturing Establishments for Perampanel Tablets**

Manufacturing information is reproduced from the attachment to Form 356h.

**Drug Substance Manufacturer:**

**Eisai Co., Ltd.**  
Kashima Plant,  
22 Sunayama, Kamisu-shi  
Ibaraki-ken, 314-0255  
Japan

FEI No: 3002806886

Responsibility: Manufacturing including (b) (4) packaging, release testing,  
stability testing

Contact Person: Kiyoshi Moriya, QA Manager  
Telephone: 81-479-46-1157  
Fax: 81-479-46-4969

Site is ready for inspection.

**Drug Product Manufacturer:**

**Eisai Co., Ltd.**  
Kawashima Factory  
1 Kawashimatakehaya-machi  
Kakamigahara  
Gifu 501-6195  
Japan

FEI No: 3004967045

Responsibility: Manufacture (bulk tablets), bulk packaging, quality control, release  
testing

Contact Person: Ryusuke Sasaki, Director QA  
Telephone: 81-586-89-4706  
Fax: 81-586-89-5291  
E-mail: r-sasaki@hhc.eisai.co.jp

Site is ready for inspection.

**Eisai, Inc.**  
RTP Campus  
900 Davis Drive  
Research Triangle Park, NC  
27709  
USA

FEI No.: 3001753294

Responsibility: Final packaging, quality control, release testing, stability testing

Contact Person: Lynn Poplin, Director Quality Systems  
Telephone: 919-941-7282  
Fax: 919-941-0660  
E-mail: Lynn\_Poplin@eisai.com

Site is ready for inspection.

**Pharma Packaging Solutions**  
A Division of Carton Service Inc.  
101 First Quality Drive  
P.O. Box 1219  
Norris, TN  
37828  
USA

FEI No.: 3002763532

Responsibility: Final packaging

Contact Person: David P. McNally, Director of Regulatory Affairs and Quality Assurance  
Telephone: 865-494-1124  
Fax: 865-494-6050  
E-mail: DMcNally@PharmaPackSol.com

Site is ready for inspection.

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR A NEW NDA/BLA**

<b>NDA Number:</b> 202-834	<b>Supplement Number and Type:</b> N/A	<b>Established/Proper Name:</b> Perampanel Tablets
<b>Applicant:</b> MAP Pharmaceuticals	<b>Letter Date:</b> 25-May-2011	<b>Stamp Date:</b> 25-May-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	N/A		
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion claimed.

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	N/A		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	12-Jan-2011	
	IV			14-Jul-2008	
	III			28-May-2010	
	III			28-May-2010	
	III			01-Jun-2010	
	III			27-May-2010	
	III			30-Sep-2010	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	Is the product quality section of the application fileable?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	N/A		Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			Describe potential review issues here or on additional sheets

*{See appended electronic signature page}*

Martha R. Heimann, Ph.D.  
CMC Lead, DNDQA-1, ONDQA

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief, DNDQA-1, ONDQA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARTHA R HEIMANN  
06/16/2011

RAMESH K SOOD  
06/20/2011