CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-827

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-872 SUPPL # HFD # 120

Trade Name Keppra Injection

Generic Name Levetiracetam

Applicant Name UCB, Inc.

Approval Date, If Known July 31, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE 3

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 ☐

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.

In addition to the bioequivalence studies, the company conducted safety and tolerability studies. According to the medical officer, the safety studies were required and the absence of their safety information would result in an unsafe label.

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:

Safety information regarding an intravenous Keppra - a new formulation

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 ☒ NO ☐

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

NDA# 21-035 Keppra Tablets

NDA# 21-505 Keppra Oral Solution

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 ☐

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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 ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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:

N01165 - Randomized, single blind, placebo controlled, parallel study to assesss the pharmacokinetics and safety of Keppra injection - a dose escalation study, 2000 - 4000 mg IV, administered over 15 mins and 1500 - 2500 mg IV administered over 5 mins.

N01166 - multi-center, open label study evaluating the saftey and tolerability of levetiracetam - 15 mins IV infusion in doses ranging from 1000mg - 3000mg a day admininstered BID as adjucntive treatment for 4 days.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☒

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

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 ☒

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

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"):

N01165 - Randomized, single blind, placebo controlled, parallel study to assesss the pharmacokinetics and safety of Keppra injection - a dose escalation study, 2000 - 4000 mg IV, administered over 15 mins and 1500 - 2500 mg IV administered over 5 mins.

N01166 - multi-center, open label study evaluating the saftey and tolerability of levetiracetam - 15 mins IV infusion in doses ranging from 1000mg - 3000mg a day admininstered BID as adjucntive treatment for 4 days.

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 # 68,187	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain: Not sure if N01166 was submitted under the IND, but UCB was the sponsor

(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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

Name of person completing form: Courtney Calder
Title: Project Manager
Date: July 26, 2006

Name of Office/Division Director signing form: Rusty Katz, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Russell Katz
7/31/2006 06:05:13 PM

MEMORANDUM	Division of Medication Errors and Technical Support Office of Drug Safety HFD-420; WO22, Rm. 4447 Center for Drug Evaluation and Research

To: Russell Katz, MD
Director, Division of Neurology Products, HFD-120

From: Tina M. Tezky, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Through: Alina R. Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: February 28, 2005

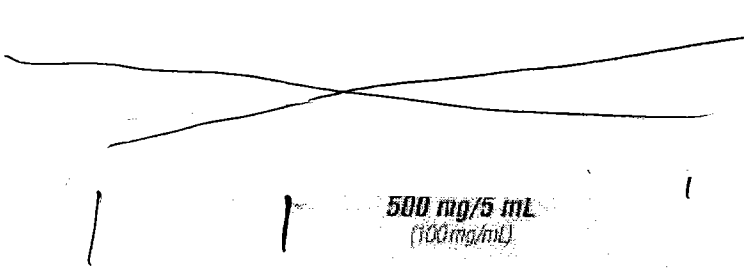
Re: ODS Consult #05-0013-1; Keppra (levetiracetam) Injection; NDA 21-872

This memorandum is in response to the February 6, 2006 request from your Division for a review of the revised labels and labeling for Keppra. DMETS reviewed the labels and labeling for Keppra Injection on September 1, 2005 (ODS consult 05-0013). These revised labels and labeling are in response to our comments. Following our review we offer these additional recommendations.

A. GENERAL COMMENTS

1. The proprietary name, established name, and strength should be the most prominent information on the principle display panel.

2. Use one color for the established name and dosage form "levetiracetam injection".



B. CONTAINER LABEL

1. See General Comments A.2.

2. Revise the statement "[redacted]" to read: "Must be diluted prior to administration".

C. CARTON LABLELING

1. See General Comments A.1 and A.2.

2. "[redacted]" Please relocate these warnings to below the expression of strength.

3. Revise the statement "[redacted]" to read "Must be diluted prior to administration". "[redacted]" It should be presented below the "For intravenous use only" statement.

D. PACKAGE INSERT LABELING

No comments at this time.

In summary, DMETS recommends implementation of the label and labeling revisions outlined above. DMETS 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 Diane Smith, Project Manager at 301-796-3242.

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/s/

Tina Tezky
3/30/2006 05:30:45 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/31/2006 08:17:27 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/31/2006 08:37:58 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-872

UCB Pharma, Inc.
Attention: Linda Noa
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Noa:

Please refer to your December 20, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Keppra Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 21, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Melina Griffis, R.Ph., Sr. Regulatory Project Manager, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
2/18/05 08:21:47 AM

Calder, Courtney

om: Tezky, Tina
ent: Tuesday, July 25, 2006 1:53 PM
To: Calder, Courtney
Cc: Claffey, David; Feeney III, John J; Holquist, Carol A; Toyer, Denise P; Smith, Diane; Mahmud, Alina
Subject: RE: Keppra IV labeling

Hi Courtney,

We acknowledge that the sponsor revised the container and carton labeling per our recommendations. However, the concentration (100 mg/mL) on the container label appears very faint and is difficult to read. DMETS recommends increasing the font size and/or bolding to improve readability.

Please call if you have any questions.

Thanks,

Tina

From: Calder, Courtney
Sent: Tuesday, July 25, 2006 9:07 AM
To: Claffey, David; Feeney III, John J
Cc: Tezky, Tina
Subject: RE: Keppra IV labeling

Hi David,
DMETS said they would get back with me today or tomorrow re: the newest carton and container labeling.

Hi Tina - Please see David's thoughts, below. Thanks, Courtney

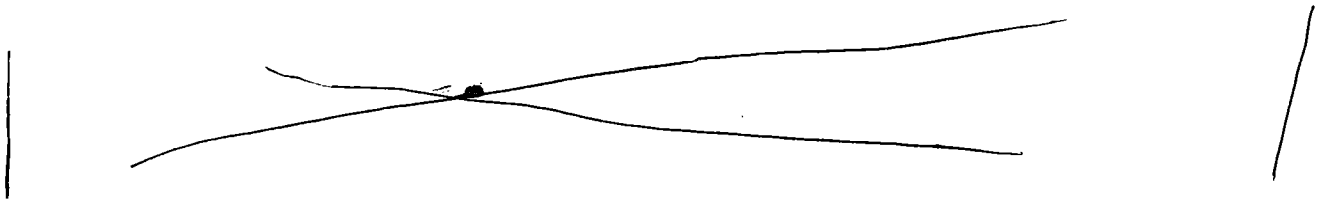
---

From: Claffey, David
Sent: Monday, July 24, 2006 6:15 PM
To: Feeney III, John J
Cc: Calder, Courtney
Subject: RE: Keppra IV labeling

Yes I am John. I will get back to you in the morning about it.

Do you know if DMETS sent anything to the applicant in the last few weeks? I am trying to get a handle on the required format of the established name on the carton labels. I think that they may need to read:

Keppra
(levetiracetam) injection



From: Feeney III, John J
Sent: Monday, July 24, 2006 5:28 PM

To: Calder, Courtney
Cc: Claffey, David
Subject: RE: Keppra IV labeling

Hi David, Are you still working on anything for IV diastat?

From: Calder, Courtney
Sent: Monday, July 24, 2006 9:19 AM
To: Feeney III, John J
Cc: Claffey, David
Subject: RE: Keppra IV labeling

Hi John,
Yes, they responded in May, and I think David Claffey has been reviewing their response.

Also, to get the the EDR most of the time now you have to type in the whole address (http://edr.cder.fda.gov/), the "EDR" shortcut does not always work.

I will start working on an approval letter/package.

Thanks, Courtney

From: Feeney III, John J
Sent: Sunday, July 23, 2006 5:19 PM
To: Calder, Courtney
Subject: Keppra IV labeling

Hi, Can you take a few minutes Monday AM to try to address an IV Keppra issue. We probably need to figure it out before we can take a final action. The issue is a carton and container labeling one. Did the March 2006 DMETS comments ever get sent to UCB? If they were, can you find out if UCB ever responded (EDR isn't working for me today, so I can't see what has come in recently)?

Thanks, John

Calder, Courtney

To: Noa Linda
Subject: NDA 21-872

Hi Linda,
We acknowledge receipt on Feb. 1, 2006, of your January 31, 2006, resubmission to your new drug application for Intravenous Keppra (levetiracetam)

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is August 1, 2006.

Sincerely, Courtney

****

Courtney R. Calder, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neurology Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1050
Fax: (301) 796-9842
Email: courtney.calder@fda.hhs.gov

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/s/

Courtney Calder
3/3/2006 05:27:29 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-805/Microbiology			FROM: HFD-120/Division of Neuropharmacological Drug Products	
DATE: July 20, 2005	IND NO.:	NDA NO.: 21-872	TYPE OF DOCUMENT : NDA: request for teleconference	DATE OF DOCUMENT: July 14, 2005
NAME OF DRUG: Keppra Injection	PRIORITY CONSIDERATION: standard		CLASSIFICATION OF DRUG: Anti-Convulsant	DESIRED COMPLETION DATE: Hold the teleconference in the next couple weeks?
NAME OF FIRM: UCB Pharma				

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the sponsor's microbiology proposals and provide any necessary feedback.

The review chemist is David Claffey, PhD

Please let me know if you would like me to help set up a teleconference.

Thank you

SIGNATURE OF REQUESTER: Courtney Calder (x45528) calderc@cder.fda.gov	METHOD OF DELIVERY (Check one): MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Courtney Calder
7/20/05 01:58:06 PM

Calder, Courtney

To: mary.alonso@ucb-group.com
Subject: NDA 21-872 (Keppra Injection)

Dear Ms. Alonso,
This email is to inform you that we received your July 14, 2005 request for a type C meeting to discuss a CMC supplement and have granted the meeting. The meeting details are
below:
Telecon
Date: August 9, 2005
Time: 3:30 - 4:00 pm

Sincerely,
Courtney

****

Courtney R. Calder, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 594-5528
Fax: (301) 594-2859
Email: calderc@cder.fda.gov

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/s/

Courtney Calder
7/26/05 12:43:22 PM