CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203993Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203993 SUPPL # HFD #

Trade Name Onfi

Generic Name clobazam oral suspension (2.5mg/mL)

Applicant Name Lundbeck LLC

Approval Date, If Known December 14, 2012

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) NDA

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.

New Dosage Form indication based on bioequivalence study data.

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:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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# NDA 202067 Onfi (clobazam) Tablets

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:

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"):

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

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

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

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

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

Investigation #1	!
	!
YES ☐	! 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: Su-Lin Sun, PharmD
Title: Senior Regulatory Project Manager
Date: December 14, 2012

Name of Office/Division Director signing form: Russell G. Katz, MD
Title: Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

SU-LIN SUN
12/14/2012

RUSSELL G KATZ
12/14/2012

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: **203993** Supplement Number: **N/A** NDA Supplement Type: **3**

Division Name: **Neurology Products** PDUFA Goal Date: **12/28/2012** Stamp Date:

Proprietary Name: **Onfi**

Established/Generic Name: **clobazam**

Dosage Form: **oral suspension (2.5mg/mL)**

Applicant/Sponsor: **Lundbeck LLC**

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
N/A

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): **1**
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

_____

Su-Lin Sun, Pharm D, Senior Regulatory Project Manager

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

/s/

SU-LIN SUN
12/11/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDAs 202067 and 203993

Lundbeck
Attention: Tom Stothoff
4 Parkway North, Suite 200
Deerfield, IL 60015

Re: Request for a Waiver for Certain Postmarket Reporting Responsibilities Under 21 CFR 314.80

Dear Mr. Stothoff:

In your letter dated February 28, 2013, you requested that Lundbeck be waived of certain of its post-marketing periodic safety reporting responsibilities under 21 CFR 314.80 for its two approved new drug applications (NDAs) for clobazam, NDA 202067 Onfi (clobazam) tablets and 203993 Onfi (clobazam) oral suspension.

Waiver request #1 – format of the periodic safety report

In your February 28, 2013, letter, you have proposed that, in lieu of submitting your postmarket periodic safety report in the format of a Periodic Adverse Drug Experience Report (PADER) as required under our present regulations at 21 CFR 314.80, you be allowed to submit an international Periodic Safety Update Report (PSUR) for Onfi oral suspension (U.S. approval granted December 14, 2012).

In e-mail correspondences dated March 5, 7, and 12, 2013, with Mr. Jeffrey Trunzo of my staff, you modified your request. You proposed to include the postmarket safety information for Onfi oral suspension in the PSUR you submit for Onfi tablets (combined PSUR). This PSUR is submitted every 6-months (October 20 and April 20 DLPs) through October 20, 2014 and annually thereafter (October 20 DLP), as described in our December 7, 2011 waiver letter that allowed Lundbeck to submit a PSUR in place of the PADER for the tablet formulation.

Waiver request #2 – timing of the periodic safety report

You noted that under our current regulations quarterly reporting is required for the oral suspension formulation through December 14, 2015, the 3-year post-approval point for the product. You have requested a waiver of this requirement and proposed to submit the information for the oral suspension formulation every six months for the first three years following the December 14, 2012, U.S. approval.

Therefore, you would submit a 6-month combined PSUR beginning with the reporting period from October 21, 2012 to April 20, 2013 through the reporting period covering April 21, 2015 to October 20, 2015. You would then submit a PSUR Addendum Report for NDA 203933 covering an approximately 2-month period from October 21, 2015 to December 13, 2015 to fulfill the reporting requirements under 21 CFR 314.80(c)(2)(i) and 314.80(c)(2)(ii)(a) for this NDA.

The first annual combined PSUR would cover the reporting period from October 21, 2015 to October 20, 2016. Subsequent annual PSURs would cover the period from October 21 to October 20 of the following year. The combined PSUR would be submitted within 60 calendar days of the DLP.

Based upon our review of the proposals stated in your letter, and in your e-mail correspondence with my staff, I concur that these modifications to your post-marketing periodic safety reporting requirements are acceptable at this time for the following approved applications:

NDA 202067	Onfi (clobazam) tablets
NDA 203993	Onfi (clobazam) oral suspension

In accordance with 21 CFR 314.90(b), your waiver requests #1 and #2 are granted and effective as of the date of this letter, provided that you continue to adhere to the conditions in our December 7, 2011, letter, and in the conditions listed below. Detailed responses to your requested waivers are described below:

Response to waiver requests #1 and #2

For the above-listed approved NDAs, you may substitute your combined PSUR for the PADER required and described at 21 CFR 314.80(c)(2) and may submit the combined PSUR according to the schedule you proposed, provided all seven of the following conditions are met:

(1) The combined PSUR is prepared according to the guideline developed by the International Conference on Harmonisation (ICH) designated as ICH-E2C and published in the Federal Register on 19 May 1997 [62 FR 27470] and the Addendum to E2C published in the Federal Register on 05 February 2004 [69 FR 5551].

(2) The Addendum Report is prepared according to the guidelines designated as Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and published in the Federal Register on 5 February 2004 [69 FR 5551]. The Addendum Report includes a narrative summary and analysis of the information in the report and an analysis of the 15-day "Alert reports" submitted during the reporting interval so that the Addendum Report contains all of the post-marketing safety information required under 21 CFR 314.80(c)(2)(ii) for a periodic adverse drug experience report.

(3) The combined PSUR for these products is submitted every six months (October 20 and April 20 DLPs) for the first three years following the December 14, 2012, U.S. approval date for NDA 203993. Thus, a 6-month combined PSUR

will be submitted within 60 calendar days following the April 20 and October 20 DLPs, for the following 6-month periods:

- October 21, 2012 to April 20, 2013
- April 21, 2013 to October 20, 2013
- October 21, 2013 to April 20, 2014
- April 21, 2014 to October 20, 2014
- October 21, 2014 to April 20, 2015
- April 21, 2015 to October 20, 2015

Beginning with the period from October 21, 2015 to October 20, 2016, and thereafter, the combined PSUR for these products will be submitted on an annual basis within 60 calendar days following the October 20 DLP.

(4) A PSUR Addendum Report for NDA 203993 covering an approximately 2-month period from October 21, 2015 to December 13, 2015, will be submitted within 30 calendar days following the December 13, 2015 DLP.

(5) The combined PSUR is comprised of two parts, the descriptive portion and the individual case safety reports, and each part may be submitted electronically or on paper. All electronic submissions are made through the Gateway, and all paper submissions should be sent to:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

(a) Descriptive portion

You submit the descriptive portion of the combined PSUR to NDA 202067 and NDA 203993.

If you are submitting the descriptive portion electronically, please see the website on the electronic common technical document (eCTD) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

If you are submitting the descriptive portion on paper, you must submit two copies of the PSUR.

(b) Individual case safety reports

You submit, at the time you submit your combined PSUR, the individual case safety reports that you are required to submit as part of a periodic safety report under 21 CFR 314.80(c)(2). These include both medically confirmed and medically unconfirmed (consumer) reports. You may submit the individual case safety reports electronically or on paper.

If you are submitting your individual case safety reports electronically, you must submit them as XML files using the ICH E2B data elements. For more information on electronic submissions of individual case safety reports, please see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm.

If you are submitting your individual case safety reports on paper, you must submit them on the FDA 3500A form as described under our regulations at 21 CFR 314.80. If you are also submitting the descriptive portion on paper, attach the paper 3500A forms to each copy of the paper descriptive portion and submit the descriptive portion and the individual case safety reports together. If you are submitting the descriptive portion electronically but the individual case safety reports on paper, send two copies of each ICSR to the application (two complete sets of FDA Form 3500A).

Please do not submit in the combined PSUR any copies of individual case safety reports that were previously submitted. We do ask that you include in the PSUR a list of individual case safety reports that were previously submitted and their dates of submission.

(6) You submit, as an appendix to the combined PSUR, a tabular listing by body system of all consumer-reported adverse experience terms and counts of occurrences for individual safety cases, if such cases are not already included in the PSUR tabular listings. If not included in other listings, these lists should be segregated by classification of report (e.g., serious/unexpected; serious/expected; non-serious/unlisted; and non-serious/listed).

(7) You submit, as an appendix to the combined PSUR, a narrative that references the changes, if any, that you believe appropriate, based on the new information received in the reporting period, in your approved U.S. labeling for NDA 202067 and NDA 203993. In this appendix, please also include a copy of the most recently approved U.S. labeling for NDA 202067 and NDA 203993.

Therefore, waivers #1 and #2 outlined in this letter will be in effect until you are notified in writing that they have been discontinued. Also, please note that this letter in no way affects your other reporting responsibilities under our regulations except as specifically outlined in this letter and in our December 7, 2011, letter (e.g., this letter does not affect your expedited reporting responsibilities for adverse experiences that are both serious and unlabeled).

If you have any questions, please contact Mr. Jeffrey Trunzo, Regulatory Analyst at (301) 796-2380.

Sincerely,

{See appended electronic signature page}

Gerald Dal Pan, M.D., M.H.S.
Director
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

GERALD J DALPAN
04/15/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203993 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Onfi Established/Proper Name: clobazam Dosage Form: oral suspension (2.5mg/mL)		Applicant: Lundbeck LLC Agent for Applicant (if applicable): Thomas Stothoff
RPM: Su-Lin Sun, PharmD		Division: Neurology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☑ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is December 28, 2012 (actual approval date is 12/14/2012)	☑ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☑ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☑ Standard ☐ Priority
Chemical classification (new NDAs only): 3

☐ Fast Track
☐ Rolling Review
☑ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☑ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☑ Yes ☐ No
• Press Office notified of action (by OEP)	☑ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☑ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☑ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☑ Yes If, yes, NDA # 202067 and date exclusivity expires: October 21, 2018
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☑ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☑ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE (Section 1)	
❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List (Section 2)	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☑ Included
Documentation of consent/non-consent by officers/employees	☑ Included
Action Letters (section 3)	
❖ Copies of all action letters *(including approval letter with final labeling)*	NDA ACK LTR 03/06/12 Filing LTR 5/9/12 Action LTR 12/14/2012
Labeling (section 4)	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	November 28, 2012
• Original applicant-proposed labeling	Feb 28, 2012
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☑ Medication Guide ☑ Patient Package Insert ☑ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	see Package insert section
• Original applicant-proposed labeling	See package insert section
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	02/28/12 (Lundbeck's submission) 11/16/12 Lundbeck's submission
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Reviewed under NDA 202067 Onfi (clobazam) tablet –please see NDA 202067 file
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☑ RPM May 7, 2012 ☑ DMEPA Oct 29, 2012 ☑ DMPP/PLT (DRISK) Nov 16, 2012 ☑ ODPD (DDMAC) Nov 20, 2012 ☑ SEALD 12/13/2012 ☑ CSS 12/14/2012
Administrative / Regulatory Documents (Section # 5)	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM filing review—April 12, 2012 ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☑ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☑ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☑ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan indication—PREA waived • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☑ Included --December 11, 2012

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☑ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	see electronic correspondences
❖ Internal memoranda, telecons, etc.	See electronic correspondences
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☑ No meeting
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☑ no meeting
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☑ No meeting
• EOP2 meeting *(indicate date of mtg)*	☑ No meeting
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☑ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos (Section # 6)	
❖ Office Director Decisional Memo *(indicate date for each review)*	☑ None
Division Director Summary Review *(indicate date for each review)*	☑ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	12/12/12
PMR/PMC Development Templates *(indicate total number)*	☑ None
Clinical Information[6] (Section # 7)	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	12/12/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☑ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Please see clinical review memo
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☑ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☑ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☑ None

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☑ None
Clinical Microbiology ☑ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☑ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology (Section 8) ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☑ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	See reviewer's memo
Clinical Pharmacology review(s) *(indicate date for each review)*	Clin Pharm Review—12/08/12 Clin Pharm Filing--12/08/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	BE inspection report –11/01/12 Memo for filing—05/03/12
Nonclinical ☑ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality (Section 9) ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☑ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	Filing review 4/23/12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	11/9/2012 12/12/12-CMC Memo to File
❖ Microbiology Reviews ☑ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	11/7/12—general review 3/20/12—general review 3/2/12—filing review
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☑ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☑ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	See CMC review
☐ Review & Environmental Impact Statement *(indicate date of each review)*	See CMC review
❖ Facilities Review/Inspection	
☑ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 04/18/2012 (see CMC review memo) ☑ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: N/A ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☑ Completed (see CMC review memo) ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

/s/

SU-LIN SUN
12/18/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, December 13, 2012 5:07 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 FDA's proposed Onfi PI-MG-IFU

Importance: High

Attachments: NDA 203993 ONFI oral suspension--FDA's proposed -Final PI-MG-IFU --121312.doc

Dear Tom:

Based on our SEALD team's recommendation, I made several modifications:

1.Removal of the header will allow HL to meet the 1/2 page requirement. The numbered lines should also be removed throughout the PI.
2. Because this product has a Medication Guide, the correct statement should be: "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide". The Labeling Review Tool states that when there are two pieces of FDA-approved patient labeling, the MG takes precedence.
3. The title for 7.3 in the TOC reads: "(b) (4), CNS Depressants and Alcohol" while 7.3 in the FPI reads: "CNS Depressants and Alcohol".
4. The format for cross-referencing is correct in the FPI, however, many citations are incorrect. For example, in 5.3, the cross-reference should be 2.2 instead of 2.6. Many citations were not updated to reflect the new ordering of subsections in D&A; also see 8.5, 8.6, 8.7, 8.8, 9.3, 12.3 (under Age and Hepatic Impairment), 12.5 and 17 (under Increasing or Decreasing the Onfi Dose). Recommend review of entire PI for correct cross-references
5. Post Marketing Adverse reaction section--delete first sentence.
6. delete (b) (4)@ end of the PI. Per SEALD team's recommendation, the only date in the PI should be the "Revised date" in HL section.

Please double check the cross-reference # throughout the PI again and make any edits if needed (with track changes).

NDA 203993 ONFI oral suspensio...

Thanks,
Sulin

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/s/

SU-LIN SUN
12/14/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, December 12, 2012 2:21 PM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 oral syringe timeline

OK, thank you, I will inform our review team. :-)

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Wednesday, December 12, 2012 1:53 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 oral syringe timeline

Dear Sulin,

We expect to receive the new syringes with the requested statements printed on the barrel in the April 2013 timeframe. The new syringes will be used immediately upon receipt and any original syringes still on hand will be discarded.

It will likely be around June 2013 when product being released to the market would include the new syringes.

As stated in our Nov 8 email, we expect to only use the original syringe in approximately the first 7 commercial batches.

Regards,
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Tuesday, December 11, 2012 3:41 PM
To: Thomas Stothoff
Subject: RE: NDA 203993 oral syringe timeline
Importance: High

Dear Tom:

Our DMEPA review team would like Lundbeck to confirm the estimated timeline when the initial launch batch oral syringes will be replaced with the FDA's requested new oral syringes with the requested statements printed on the barrel (within 3 months or 6 months post NDA 203993 approval date).

thanks,
Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Friday, November 09, 2012 11:59 AM
To: Sun, Su-Lin
Cc: Jane M. Stachura
Subject: Re: NDA 203993 container and carton comments

Thanks Sulin
I will try and file amendment on Monday. Tues at latest but I think we should be able to file on Monday.
Tom

Sent from my iPhone

On Nov 9, 2012, at 10:55 AM, "Sun, Su-Lin" <Su-Lin.Sun@fda.hhs.gov> wrote:

> Dear Tom or Jane:
>
> Below are the response from our review team:
>
> **1. Please submit the carton and container revisions now since these are independent from the other labeling (PI, MG, IFU) so that we can approve these items early and avoid the rush of the approaching action date.**
>
> **2. Yes, it is acceptable to provide the originally proposed oral syringes for the launch of the product. However, we would request you attempt to expedite an order for oral syringes with the requested statements and start providing these syringes with the product as soon as they are available.**
>
> ---
>
> **From:** Thomas Stothoff [TOMS@Lundbeck.com]
> **Sent:** Thursday, November 08, 2012 6:13 PM
> **To:** Sun, Su-Lin
> **Subject:** RE: NDA 203993 container and carton comments
>
> Hi Sulin,
>
> Should I submit a labeling amendment now for the revised label and carton to incorporate these changes? Or can I hold off until we receive comments on the package insert-MG-IFU later this month and file all revised labeling pieces together at that time?
>
> Regarding the syringes, we have already ordered syringes to support manufacturing of launch batches (approximately 7 batches). The lead time for ordering new syringes with the requested statements printed on the barrel can be up to 6 months, but we will attempt to expedite the order. Will FDA allow us to package the launch batches with the syringes without the requested statements?
>
> Regards,
> Tom

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/s/

SU-LIN SUN
12/12/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, December 11, 2012 3:50 PM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 Onfi -FDA's counter proposal PI-MG-IFU---121112
Importance: High
Attachments: NDA 203993 ONFI oral suspension--FDA's proposed PI-MG-IFU --121112.doc

Dear Tom:

1. Attached is our counter proposal for PI-MG-IFU for NDA 203993 Onfi (clobazam) oral suspension.

FYI--in Highlight section, I have consulted our SEALD team that under the section "Major Recent Change" should reflect section 2.3 (instead of 2.1). Also on the PI text section---for section 2.3--it required a vertical left line to reflect such changes.

The rest of changes are in track changes.

2. There will be no PMR or PMC for your NDA 203993.

If you have any question, please feel free to contact me.

thanks,
Sulin

From: Sun, Su-Lin
Sent: Monday, December 10, 2012 9:44 PM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 Onfi Lundbeck's counter proposal #3 PI-MG-IFU---121012

Thanks :-)

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Monday, December 10, 2012 6:59 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi Lundbeck's counter proposal #3 PI-MG-IFU---121012

Hi Sulin,

Here is our next counter proposal. Sorry this came a little late.

Tom

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Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, December 11, 2012 3:53 PM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 Onfi---Final Bottle Label and Carton

Thank you :-)

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Tuesday, December 11, 2012 3:45 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi---Final Bottle Label and Carton

Hi Sulin,
Will do. I'll submit carton and bottle label tomorrow. I guess the gateway has been down since Saturday when FDA implemented an upgrade so I hope it will be back up and running by tomorrow.
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Tuesday, December 11, 2012 2:22 PM
To: Thomas Stothoff
Subject: RE: NDA 203993 Onfi---Final Bottle Label and Carton

Can you officially submit your updated bottle label and carton label to NDA 203993 (from your 12/3/12 email)? So we will have official record from Lundbeck.
I will send you our counter-proposal for the PI within 30 minutes :-)

thanks,
Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Monday, December 03, 2012 5:48 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi---Final Bottle Label and Carton

Hi Sulin,

Attached are the updated bottle label and carton per your request.

Regards,
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, December 03, 2012 3:17 PM
To: Thomas Stothoff
Subject: RE: NDA 203993 Onfi---Lundbeck's counter proposal draft PI/MG/IFU

Will you send me your final carton and container draft, so I can forward to DMEPA and Patient Labeling and CMC for their final approval.

thanks,

Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Monday, December 03, 2012 2:22 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi---Lundbeck's counter proposal draft PI/MG/IFU

Dear Sulin,

Attached is our counter proposal for the labeling. The PI/MG/IFU have been combined into a single file per FDA request. Our response to FDA's latest comments on food effect are imbedded in the file. We look forward to FDA's feedback.

Regards,
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, November 28, 2012 3:45 PM
To: Thomas Stothoff
Subject: NDA 203993 Onfi---FDA's proposed draft PI/MG/IFU + FDA's comment on no food effect study
Importance: High

Dear Tom:

Attached are our proposed draft PI/MG/IFU, please accept all track changes that you agree with us and use track change to add your counter-proposed comments.
For the Medication Guide (MG) and Instruction for Use (IFU), please use the attached document as based document--since patient labeling team has specific format requirement. Please merge the MG and IFU to be placed at the end of PI, so all three documents will be merge as a single document.

The review team also provide their comments for your justification for not repeating a food effect study. Please send your response to us as soon as you can, no later than 11/30/12. The review team will need to decide whether a PMR will be needed or not based on your response.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD

LCDR, United States Public Health Service

Regulatory Project Manager

Food and Drug Administration

Office of Drug Evaluation I – Division of Neurology Products

Bldg. 22, Room 4209

10903 New Hampshire Ave

Silver Spring, MD 20993

Office: 301-796-0036

Fax: 301-796-9842

Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
12/11/2012

Sun, Su-Lin

From: Thomas Stothoff [TOMS@Lundbeck.com]
Sent: Wednesday, December 05, 2012 5:18 PM
To: Sun, Su-Lin
Subject: RE: Revised IFU picture--change request
Attachments: LB-2196__LiquidDosingImage_2.jpg.jpg

OK. Here is the revised picture. We should have the entire PI/MG/IFU to you tomorrow a.m.
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, December 05, 2012 2:37 PM
To: Thomas Stothoff
Subject: RE: Revised IFU picture--change request
Importance: High

Dear Tom

Our review team requests your team to move the oral syringe over a little bit more so that none of the lip is showing then it would be perfect. Their concern here is that it still doesn't quite look like it's in "the corner of the mouth".

thanks,

Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Wednesday, December 05, 2012 1:52 PM
To: Sun, Su-Lin
Subject: Revised IFU picture

Hi Sulin,
Attached is the revised picture with the syringe pointed more toward the corner of the mouth. We are moving forward with revising the IFU with this picture.
Regards,
Tom

From: Thomas Stothoff
Sent: Wednesday, December 05, 2012 11:10 AM
To: 'Sun, Su-Lin'
Subject: RE: NDA 203993 Onfi FDA's 2nd proposal for PI/MG/IFU

OK. Thanks

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, December 05, 2012 11:00 AM
To: Thomas Stothoff
Subject: RE: NDA 203993 Onfi FDA's 2nd proposal for PI/MG/IFU

If tomorrow by noon--will be fine with me, so I can show it to the team during our afternoon meeting.

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Wednesday, December 05, 2012 11:59 AM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi FDA's 2nd proposal for PI/MG/IFU

We hope to have the revised IFU by end of today. Worst case tomorrow.
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, December 05, 2012 10:52 AM
To: Thomas Stothoff
Subject: RE: NDA 203993 Onfi FDA's 2nd proposal for PI/MG/IFU

OK, thank you :-)

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Tuesday, December 04, 2012 11:40 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi FDA's 2nd proposal for PI/MG/IFU

Thanks Sulin,

I will get back to you ASAP on timing for being able to provide a revised IFU with the revised picture. Our team is meeting Wed at 1pm but I will try and get you an answer even before then. Our team is returning from AES today so should be easier to address questions such as these.

We will also plan to provide you our counter proposal #2 by COB Wed.

Regards,
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Tuesday, December 04, 2012 3:50 PM
To: Thomas Stothoff
Subject: NDA 203993 Onfi FDA's 2nd proposal for PI/MG/IFU
Importance: High

Dear Tom:

Attached the proposed PI/MG/IFU for your NDA 203993 from our review team, please accept the track change if you agree with our proposal and using track changes if you have additional editing needed.
Can you give me estimate date for when will the one of the IFU photo be replaced and send it back to us for final approval?

Once we reach an agreeable final version, I will need to send the final version to SEALD team for their final approval.
So far the carton and container are OK by our DMEPA team, my CMC reviewer is on offsite training for this week. As soon as I receive his comment, I will follow up with you.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
12/11/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, December 07, 2012 3:22 PM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 Onfi FDA's proposed PI-MG-IFU---120712

Thank you :-)

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Friday, December 07, 2012 3:03 PM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Onfi FDA's proposed PI-MG-IFU---120712

Thanks Sulin,

We appreciate FDA responding to our requests for rationale for some of the changes FDA is requiring. We will provide our next version to you by COB Monday.

I;m also following up on the CMC reviewer's question on extractables.

Have a nice weekend.

Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, December 07, 2012 1:45 PM
To: Thomas Stothoff
Subject: NDA 203993 Onfi FDA's proposed PI-MG-IFU---120712
Importance: High

Dear Tom:

Attached is our proposed PI-MG-IFU for your NDA 203993, Please send your counter-proposal back to me as soon as you can, but no later than COB on Monday 12/10/12.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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SU-LIN SUN
12/07/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, December 07, 2012 12:19 PM
To: 'Thomas Stothoff'
Subject: RE: CMC Amendment - Extractables/Leachables
Importance: High

Dear Tom:

Below is the CMC clarification question regard to your December 4, 2012 CMC amendment for NDA 203993 Onfi:

What is the compound at (b) (4) **that was found from the** (b) (4) **?**

Please send your response to me as soon as possible.

thanks,
Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Wednesday, December 05, 2012 5:05 PM
To: Sun, Su-Lin
Subject: RE: CMC Amendment - Extractables/Leachables

Dear Sulin,

We filed the CMC amendment this afternoon.

Regards,
Tom

From: Thomas Stothoff
Sent: Tuesday, December 04, 2012 12:01 PM
To: 'Sun, Su-Lin'
Subject: CMC Amendment - Extractables/Leachables

Hi Sulin,

We intend to file our CMC Amendment tomorrow (Dec 5) to address FDA's request from Aug 13, 2012 regarding extractables/leachables from the bottle cap and push-in-bottle-adapter (PIBA).

Regarding the labeling - are you still anticipating providing later today FDA's feedback on our counter proposal that we sent yesterday? I believe you stated the schedule was for FDA to meet this afternoon, provide comments later today and for Lundbeck to send our counter proposal #2 by end of tomorrow.

Thanks
Tom

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/s/

SU-LIN SUN
12/07/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, November 28, 2012 4:45 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 Onfi---FDA's proposed draft PI/MG/IFU + FDA's comment on no food effect study

Importance: High

Attachments: NDA 203993 ONFI (clobazam) oral suspension--FDA's proposed PI---11-2012.doc; NDA 203993 ONFI (clobazam)oral suspension--FDA's proposed MG-IFU--11-2012.doc; NDA 203993 FDA's comment--Lundbeck's justification on no food effect study--112812.pdf

Dear Tom:

Attached are our proposed draft PI/MG/IFU, please accept all track changes that you agree with us and use track change to add your counter-proposed comments.
For the Medication Guide (MG) and Instruction for Use (IFU), please use the attached document as based document--since patient labeling team has specific format requirement.
Please merge the MG and IFU to be placed at the end of PI, so all three documents will be merge as a single document.

The review team also provide their comments for your justification for not repeating a food effect study. Please send your response to us as soon as you can, no later than 11/30/12. The review team will need to decide whether a PMR will be needed or not based on your response.


NDA 203993 ONFI (clobazam) ora...


NDA 203993 ONFI (clobazam)oral...


NDA 203993 FDA's comment--Lund...

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD

LCDR, United States Public Health Service

Regulatory Project Manager

Food and Drug Administration

Office of Drug Evaluation I – Division of Neurology Products

Bldg. 22, Room 4209

10903 New Hampshire Ave

Silver Spring, MD 20993

Office: 301-796-0036

Fax: 301-796-9842

Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
11/28/2012

Sun, Su-Lin

From: Thomas Stothoff [TOMS@Lundbeck.com]
Sent: Friday, November 02, 2012 12:42 PM
To: Sun, Su-Lin
Subject: RE: Stability date for the labeling

Hi Sulin,
Acknowledging receipt. I will look into and get back to you early next week - hopefully Monday.
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, November 02, 2012 10:54 AM
To: Thomas Stothoff
Subject: Stability date for the labeling
Importance: High

Dear Tom:

On your proposed PI for NDA 203993 Onfi oral suspension, section # 16

ONFI oral suspension is a berry flavored off-white liquid supplied in a bottle with child-resistant closure. The oral suspension is packaged with a dispenser set which contains two calibrated oral dosing syringes and bottle adapter. Store the oral suspension in an upright position. Use within 90 days of first opening the bottle, then discard any remainder…

The original proposed PI has (b) (4) then changed by (b) (4) (someone from Lundbeck) to 90 days.

Per our Microbiology and CMC team that the antimicrobial effectiveness testing submitted with Onfi application only goes out 28 days.

Therefore, in order for the review team to consider the new proposed shelf life of 90 days, then you will need to submit new AET testing data that supports a 90 days shelf life for the open bottle. If you do have such data, please send it to me via email first as soon as possible, then officially submit to NDA 203993, so I can forward to our review team for them to review.

Thanks,

Sulin

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/s/

SU-LIN SUN
11/02/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, October 29, 2012 6:13 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 container and carton comments

Importance: High

Dear Tom:

Below are the labeling comments for cartoon and container for NDA 203993 Onfi oral suspension:

Container Label and Carton Labeling:

1. Increase the prominence of the statement “For Oral Administration” on the principal display and side panels by bolding and/or adding more white space around this statement (or by some other means) to help highlight this important information and minimize the potential for wrong route medication errors.

2. Revise the phrase [redacted] (b) (4) ” on the principal display panel to read “Instructions for Use” to reflect the correct name of the document.

3. Remove the hyphen and revise the Storage statement to read “Store at 68ºF to 77ºF (20ºC to 25ºC)” rather than “Store at 68-77ºF (20-25ºC)” to be consistent with current USP designations.

4. Replace the word [redacted] (b) (4) with the word “Lot” and replace the word [redacted] (b) (4) to the more commonly used term in the United States of “expiration” or “Exp”. Ensure this information is consistent on both container label and carton labeling.

D. Oral Syringe
1. Include the following statements on the barrel of the oral syringes:
“For Use with Onfi Oral Suspension Only.”
“For Oral Administration Only.”

** As it's indicated on our previous electronic communication that the above comments are consider preliminary comments, the container and carton agreement is subject to change until the final agreement reached upon NDA action day.**

We will send comments for MG and IFU at the time we send you our draft labeling by 11/28/12.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
10/29/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, October 24, 2012 11:37 AM
To: 'Mahlaqa Patel'
Cc: Thomas Stothoff
Subject: NDA 203993 Onfi CMC requested info

Dear Mahlaqa:

Please check with your team regard to our 08/13/12 biopharmaceutical information request (question 10.d) for NDA 203993 Onfi (oral suspension) and Tom's 0/20/12 electronic response that "data on the effect of density, viscosity, and pH on dissolution (will submit by Nov 30).

Our review team is requesting that is it possible for your team to submit the above requested information earlier (by mid November)?.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
10/24/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, October 01, 2012 12:27 PM
To: 'Thomas Stothoff'
Subject: RE: Onfi labeling strategy for suspension (b) (4)
Importance: High

Dear Tom:

Below are the comments from our review team for your inquiry:

1. Please refer to our draft guidance (b) (4): Nomenclature, Labeling, and Data for Evaluation" for the recommended data to support (b) (4) The guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U

2. (b) (4)

3. (b) (4)

If you have any question, please feel free to contact me.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Friday, September 14, 2012 2:39 PM
To: Sun, Su-Lin
Subject: RE: Onfi labeling strategy for suspension (b) (4)

Thanks Sulin. I hope I explained this so it is easy to understand. Let me know if you or the reviewers have any questions. If so, it may be better to discuss on the phone rather than email.
Have a nice weekend.
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, September 14, 2012 1:20 PM
To: Thomas Stothoff
Subject: RE: Onfi labeling strategy for suspension (b) (4)

Dear Tom:

Please let me check with our review team first, I will follow up with you as soon as I receive their recommendation.

thanks,
Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Thursday, September 13, 2012 7:02 PM
To: Sun, Su-Lin
Subject: Onfi labeling strategy for suspension (b) (4)

Dear Sulin,

I wanted to give you a heads up on our planned strategy for submission of a (b) (4) Following is an estimated timeline.

October 21, 2011: Tablet NDA 202067 approved for 5, 10 and 20 mg non-scored tablets.

Feb 28, 2012: Suspension NDA 203993 filed. Proposed labeling consists of a combined insert for suspension and non-scored tablets. We submitted a mark-up of the approved labeling for non-scored tablets to add language for the suspension.

(b) (4)

Dec 2012: Anticipated approval of suspension NDA 203993.

Feb 2013 [redacted] (b) (4)

Any comments on the suspension/non-scored labeling during review of NDA 203993 [redacted] (b) (4)

Do you agree with this approach?

Best regards,

Tom Stothoff

Director,
US CMC Regulatory

Tel 1-847-282-5769 (direct)
Mbl [redacted] (b) (6)

Lundbeck LLC
Four Parkway North
Deerfield, IL
60015
United States

Tel 1-800-455-1141
Fax 1-847-317-9112
www.lundbeck.com

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/s/

SU-LIN SUN
10/01/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Sunday, September 23, 2012 9:22 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 Onfi

Importance: High

Dear Tom:

Below are the information request from our review team:

As per the ICH Q6A guidance (page no. 14, Redispersibility) the time required to achieve resuspension by the indicated procedure should be clearly defined. Therefore the data that you have submitted in response to our question # 3 should have a time line by which the homogeneity was achieved.

2. Include numerical acceptance criteria for viscosity and the particle size distribution in the drug product specification. The proposed limits should be set based upon the data derived from the batches used in the bioequivalence study.

Please send the above information request as soon as you can.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
09/24/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, August 29, 2012 11:26 AM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 FDA's urgent information request
Importance: High

Dear Tom:

Thank you for your clarification.
There are no previous information request sent related to our concern about the 2 oral syringes. There are previous information request concern about the accuracy of dose measurement with the oral syringe.

As it is indicated on your proposed labeling, the maximum daily dose can be up to 40mg/day which should be further divided into BID dosing regimen. Therefore maximum single dose can be up to 20mg = 8mL.
Please provide us your rationale for including 2 oral syringes (10mL/syringe) are included in your proposed labeling and IFU.
If you have any question, please feel free to contact me.

thanks,
Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Tuesday, August 28, 2012 11:32 AM
To: Sun, Su-Lin
Subject: RE: NDA 203993 FDA's urgent information request

Dear Sulin,

This request indicates FDA has already asked us the question regarding the need for two syringes and that we responded, but didn't address the question to FDA's satisfaction. We have no record or recollection of this question being asked previously, and therefore, no record of responding. Certainly, we will provide a response this week, but could you provide more information on when this question was originally posed to us? If there is a record of FDA asking this question previously, we want to be sure our records are up to date, and more importantly, that we responded to the question.

In our July 25, 2012 amendment which provided a revised Instruction For Use, we did include a statement to FDA request #1 that the syringe is identical to the syringe used for our Sabril (vigabatrin) for Oral Solution product.

Thank you,
Tom

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, August 27, 2012 1:39 PM
To: Thomas Stothoff
Subject: NDA 203993 FDA's urgent information request
Importance: High

Dear Tom:

Below are urgent information request from our review team, please send us your response by Friday, August 31, 2012

We previously contacted you to understand your rationale for including two syringes with the Onfi Oral Suspension product, which we find may be potentially confusing to the consumer. However, in your response we were only informed that the syringes are similar to other products currently on the market without the rationale for inclusion of two syringes instead of just one. Your proposed 10 mL size syringe can accommodate the recommended maximum per dose of Onfi Oral Suspension (8 mL - according to your proposed dosing instructions). We would like to learn if your reason is due to integrity concerns with the syringes when washed in a dishwasher or other concern(s) . Please provide detailed rationale for including the two syringes with your product.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
08/29/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, August 27, 2012 2:39 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 FDA's urgent information request

Importance: High

Dear Tom:

Below are urgent information request from our review team, please send us your response by Friday, August 31, 2012

We previously contacted you to understand your rationale for including two syringes with the Onfi Oral Suspension product, which we find may be potentially confusing to the consumer. However, in your response we were only informed that the syringes are similar to other products currently on the market without the rationale for inclusion of two syringes instead of just one. Your proposed 10 mL size syringe can accommodate the recommended maximum per dose of Onfi Oral Suspension (8 mL - according to your proposed dosing instructions). We would like to learn if your reason is due to integrity concerns with the syringes when washed in a dishwasher or other concern(s) . Please provide detailed rationale for including the two syringes with your product.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
08/27/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, August 13, 2012 1:48 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 Onfi (clobazam) oral suspension-urgent information request

Importance: High
Sensitivity: Confidential

Dear Tom:

Below are the urgent information request from our review team, please send your response as soon as you can.

CMC Deficiencies:

1. *You mentioned in the report for clinical study # 14033A that the batch of clobazam suspension used for the study was P1437; however, in the description of the manufacturing process you indicated that the batch used for the relative bioavailability study was Lot # 015664. Clarify this discrepancy. If a different batch(s) (other than Lot # 015664) was used in the clinical study # 14033A, then provide the composition of the formulation for each batch, along with its batch analysis data (including dissolution, particle size distribution of the API used for this batch).*

2. *You stated in your pharmaceutical development section that drug product manufactured with batches of API with various particle size distributions did not exhibit any significant changes over time when stored at 25°C and 40°C through 6 months. Provide data to support such conclusion.*

3. *Provide data to demonstrate product homogeneity as a function of appropriate bottle shaking time range recommended in your labeling.*

4. *Provide extractable/leachable studies for the purpose of the evaluation of the container closure system particularly the bottle cap that is expected to be in contact with the drug product and the push-in bottle adapter (PIBA). Additionally, clarify if any of the stability studies were conducted using the inverted bottle position to show if there is any new degradation impurity generates from such bottle position. If you have not generated any stability data from such bottle orientation in storage, then provide data to show compatibility between the drug product and the bottle cap.*

5. *Your dosing accuracy study was found to be not acceptable by the Agency, because you have used water before the washing of the* (b) (4) *10-mL oral dispensers (syringes) and* (b) (4) *after washing the dosing device. We recommend that you provide the following:*
   - *(a) Dosing accuracy data (percent dosing accuracy) using the actual drug product before and after washing of the device (10 mL oral dispenser).*
   - *(b) Additionally, since you have revised the Onfi Oral Suspension instructions for use to indicate* (b) (4) *the revised dosing accuracy study should follow the revised label instruction with the revised dosing device.*
6. *We do not agree with your strategy for not conducting tests for the suspended particle size distribution and suspension viscosity as a part of the drug product and stability specification. It is likely that homogenizer (or other types of mixer to be used in future) may have impact on the particle size distribution of the dispersed phase and the suspending agents* (b) (4)

[redacted] (b) (4) *may vary from lot to lot and thus may result variation in viscosity of the drug product from batch to batch. Therefore, absence of such tests may lead to a drug product batch with undesirable suspended particles size that may cause differences in bioavailability and in physical attributes of the dosage form due to undesirable viscosity. Therefore, you should include these two tests (along with their analytical method description and their method validation) as a part of your drug product release and stability specification with appropriate limit (based on data generated from the clinical lot# 015664). Provide a revised stability protocol that includes particle size testing at selected time points (e.g. 12 months, 24 months).*

7. *In your list of major equipment (P.3.4) you have mentioned that either* [redacted] (b) (4) *other equivalent equipment will be used for API homogenization. However, from the given executed batch record for the lot # 015664 (used for BE study), we found that the mixer used for API mixing is "* [redacted] (b) (4) *Since no batch records are provided for other registration batch (e.g. lot # 015662, 015666 & 015668), therefore it is not clear whether or not all these batches used the same type of mixer. Unless you submit data to show that the different types of mixer/homogenizer does not have any effect on the API particle size distribution in the finished product, you should not utilize such flexibility in your manufacture. Therefore, you should use the type of mixer used for API mixing for the Lot # 015664 in your future commercial batches in absence of any such data.*

8. *Resubmit your statistical analysis (with details) using the 12 months stability data to support your proposed product self life of 24 months.*

9. *Provide particle size distribution data from the temperature cycling study.*

Biopharmaceutics Deficiencies:

10. *Since the provided data for dissolution are very limited, we have concerns whether or not your finished product would meet its required quality if the dissolution test is not included in your drug product's specifications. Additionally, failure in the conventional bioequivalence requirement for C_{max} was observed when your product was compared to the reference tablets, which further emphasizes the need for monitoring the dissolution of the drug product at batch release and on stability.*

    Therefore, the Agency is in disagreement with your proposed strategy of not conducting this routine test, which is required for all suspension products and has the following recommendation and requests for information:
    - *(a) Include the dissolution test in the finished product specifications.*
    - *(b) Provide the dissolution method report with complete data supporting the implementation of a dissolution method with discriminating capability.*
    - *(c) Provide data to show the effect of API particle size on dissolution*
    - *(d) Provide data to show the effect of suspension density, viscosity, and final pH on dissolution*
    - *(e) Provide dissolution data for the Lots # 015662, 015664, 015666 & 015668*

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration

Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
08/13/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, July 20, 2012 12:26 AM
To: 'Thomas Stothoff'
Subject: urgent FDA's information request --Onfi bottle label
Importance: High

Dear Tom:

During our review of your proposed label and labeling, we have the following concerns that we feel may contribute to a safety issue with your proposed product:

1) In Step 6 of your "Instructions for Use", you provide instructions for patients to measure their dose (b) (4) . However, since Onfi oral suspension is an "off-white liquid", we are concerned that it would be difficult for patients to discern the white layer of the plunger against the white liquid background due to a lack of visual contrast. Provide your response to this concern.

2) Provide the volume of drug that it takes to fill the space between the white plunger tip and the black layer.

3) This potential medication error may be mitigated through the use of a colored plunger that can provide the necessary visual contrast for the patient . Provide us with your feasibility assessment of this option.

Please submit your response as soon as possible, no later than COB on July 25, 2012.

If you have any question, please feel free to contact me.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
07/20/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, July 05, 2012 7:41 PM
To: 'Thomas Stothoff'
Subject: NDA 203993 PI change request

Importance: High

Dear Tom:

Below are the request from our review team for your proposed PI for NDA 203993 Onfi (clobazam oral suspension):
In the PI Section 12.3 Clinical pharmacology, the description and the findings of the BE study conducted for oral suspension should be added. Please revise your PI and send it back to us within 2 weeks. Please provide us with a clean version and also a track change version of word document.

thanks
Sulin

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/s/

SU-LIN SUN
07/05/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, May 31, 2012 2:53 PM
To: 'Thomas Stothoff'
Subject: RE: NDA 203993 Clobazam Suspension - Review of Bottle Label

Dear Tom:

Below are the comments from our review team for your request of the review of bottle label for NDA 203993 Onfi (clobazam) oral suspension:

In regard to your email inquiry vis-a- vis product labeling, dated 5/29/12, we anticipate we will comments to you sometimes from September to October of this year. However, we would like to emphasize that the labels and labeling aren't approved until an NDA application is approved, and that labeling a product prior to NDA approval is always risky since FDA can request changes up to approval of the application.

If you have any question, please feel free to contact me.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Wednesday, May 30, 2012 9:27 AM
To: Sun, Su-Lin
Subject: RE: NDA 203993 Clobazam Suspension - Review of Bottle Label

Thanks Sulin.

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, May 30, 2012 12:58 AM
To: Thomas Stothoff
Subject: RE: NDA 203993 Clobazam Suspension - Review of Bottle Label

I will check with our CMC and OSE team and as soon as I receive their recommendation, I will follow up with you.

thanks,
Sulin

From: Thomas Stothoff [mailto:TOMS@Lundbeck.com]
Sent: Tuesday, May 29, 2012 4:07 PM
To: Sun, Su-Lin
Subject: NDA 203993 Clobazam Suspension - Review of Bottle Label

Dear Sulin,

In the recently received FDA Filing Letter for NDA 203993 dated May 9, 2012 it is stated that the PDUFA review date is Dec 28, 2012 and that FDA will communicate proposed labeling by Nov 30, 2012.

In anticipation of an NDA approval at the end of 2012, Lundbeck is planning to manufacture validation/commercial batches in advance of the approval in order to support launch of the product. We obviously do not want to label the product with labels which have not been approved by FDA yet, but our contract manufacturer does not allow for storage of unlabeled vials. Nor do they allow for over-labeling (or removal of labels) in the event label changes are required.

Would it be possible to receive comments on the bottle label only in the September-October 2012 timeframe which would provide us comfort in labeling commercial product prior to NDA approval? We acknowledge that even if FDA provides comments at this earlier timeframe, there is a chance further changes could be requested by FDA, but it would be helpful to at least get initial feedback on the bottle label in that September-October 2012 timeframe.

Thank you in advance for consideration of this request.

Best regards,

Tom Stothoff

Director,
US CMC Regulatory

Tel 1-847-282-5769 (direct)
Mb (b) (6)

Lundbeck LLC
Four Parkway North
Deerfield, IL
60015
United States

Tel 1-800-455-1141
Fax 1-847-317-9112
www.lundbeck.com

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SU-LIN SUN
05/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203993

FILING COMMUNICATION

Lundbeck LLC
Attention: Thomas Stothoff
Director, US CMC Regulatory
Four Parkway North
Deerfield, IL 60015

Dear Mr. Stothoff:

Please refer to your New Drug Application (NDA) dated February 28, 2012, received February 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Onfi (clobazam) oral suspension 2.5mg/mL.

We also refer to your amendments dated March 9, 2012, March 14, 2012, and March 16, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 28, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 30, 2012.

Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

At the present time we have the following comments and requests:

Chemistry, Manufacturing and Controls

1. With regard to the manufacture of clobazam suspension, we ask you to provide data from development or engineering studies to support the proposed process control parameters and acceptance criteria.

2. The provided stability data do not support the proposed 24 month expiry. Although we will review additional stability data received prior to mid-cycle, data received later may not be reviewed during this review cycle.

3. You have provided a brief description of statistical analyses performed on the drug product stability data. We request that you provide the detailed statistical output from the statistical analysis.

Clinical Pharmacology

1. We noticed that the effect of food has not been evaluated for the proposed new formulation. Given the labeling recommendation for the oral tablets to be taken without regard to food, you need to address how the oral suspension can also be administered under the fed condition.

2. Please provide a "definition" file in PDF format for the electronic datasets for Study 14033A.

LABELING

During our preliminary review of your submitted labeling, we have identified the following labeling format issues for your proposed package insert:

Highlights

1. The Highlights must list recent major changes (RMC) in Section 2.2 of the prescribing information (e.g., administration information about ONFI oral suspension).

2. Use bulleted subheading for each dosage form type.

3. Because of the additional patient-labeling (i.e., Patients Instructions for Use), you must include the following statement in the Patient Counseling Information Statement in the Highlights following bolded verbatim statement: "See section 17 for **Patient Counseling Information** and FDA-approved patient labeling".

Full Prescribing Information

1. Remove the periods after the numbers in each Section (for example, use "4" instead of "4.").

2. If a RMC is listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

3. Please change the statement "See FDA-approved patient labeling (Medication Guide)" to "See FDA-approved patient labeling (Medication Guide and Instructions for Use)".

We request that you resubmit labeling in word document format that addresses these issues by May 28, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Su-Lin Sun, PharmD, Regulatory Project Manager, by phone or email at (301) 796-0036 or su-lin.sun@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

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

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/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
05/09/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, March 06, 2012 4:24 PM
To: 'Jeanine M. Swalec'
Subject: NDA 203993 information request-quality (micro)

Importance: High

Hi, Jenny:

Below are the information requests from our microbiology review team:

1. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the *Burkholderia cepacia* complex (Bcc).

We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for these species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of Bcc and cells that are acclimated to the product and the environments (e.g., warm or cold water) that may be tested.

2. We acknowledge that antimicrobial effectiveness testing of the drug product is performed according to USP<51> and that acceptance criteria for testing have been established. Please provide validation results for antimicrobial effectiveness testing with the preservative at or below the product's release and stability specification.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
03/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203993

NDA ACKNOWLEDGMENT

Lundbeck Inc.
Attention: Jenny Swalec
Sr. Director, Global Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product:	Onfi (clobazam) Oral suspension (2.5 mg/mL)
Date of Application:	February 28, 2012
Date of Receipt:	February 28, 2012
Our Reference Number:	NDA 203993

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).
The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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SU-LIN SUN
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