

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203993Orig1s000

CHEMISTRY REVIEW(S)

**CMC Memo to File**

| | |
|----------|-----------------------------|
| To: | NDA |
| Date | 12 December 2012 |
| Sponsor: | Lundbeck Inc. |
| Drug: | Onfi™ (clobazam) Suspension |
| Subject | Approval recommendation |
| Reviewer | Dr. Akm Khairuzzaman |

On December 05, 2012, Lundbeck has submitted a CMC amendment reporting additional findings from their ongoing extractable/leachable study that was originally asked by the CMC reviewer on August 13th, 2012. The majority of this requested data was submitted by the Applicant on August 30, October 11 and November 15, 2012. This recent amendment (dated December 5, 2012) does not change the original recommendation made in the first review and CMC recommends that NDA application 203-993 be approved.

HFD-/Division File
HFD-120

Akm Khairuzzaman, Ph.D.
Chemistry Reviewer

Martha Heimann, Ph.D.
CMC Lead, ONDQA

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/s/

AKM KHAIRUZZAMAN

12/12/2012

Recommended for approval from CMC point of view

MARTHA R HEIMANN

12/12/2012



**PRODUCT QUALITY REVIEW
CMC and Biopharmaceutics
Office of New Drug Quality Assessment**



NDA 203-993

OnfiTM (clobazam) Suspension, 2.5 mg/mL

Lundbeck Inc.

**Akm Khairuzzaman, Ph.D.
ONDQA/DNDQA1/Branch 1
CMC and Biopharmaceutics Reviewer**

Reviewed for the Division of Neurology Products, HFD-120



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CMC and Biopharmaceutics
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CMC and Biopharmaceutics Review Data Sheet

1. NDA 203-993
2. REVIEW #: 1
3. REVIEW DATE: 11/08/2012
Revised:
4. REVIEWER: Akm Khairuzzaman, Ph.D.
5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|--------------------|---------------|
| None | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|------------------------|-------------------|
| Original Submission | 28-February-2012 |
| CMC Amendment | 03-July-2012 |
| CMC Amendment | 30-August-2012 |
| CMC Amendment | 27-September-2012 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|-----------------------|--|
| Name | Lundbeck Inc. |
| Address | 4 Parkway North Suite 200 Deerfield, IL 60015, USA |
| Representative | Jenny Swalec |
| Telephone | (847) 282-1066 |
| FAX Number | N/A |

8. DRUG PRODUCT NAME/CODE/TYPE:

| | |
|------------------------------------|--------------------|
| Proprietary Name | Onfi TM |
| Non-Proprietary Name (USAN) | Clobazam |
| Code Names | N/A |
| Chemistry Type | 5 |
| Submission Priority | S |

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Benzodiazepine.
11. DOSAGE FORM: Suspensions
12. STRENGTH/POTENCY: 2.5 mg/mL
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

 X Not a SPOTS product

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

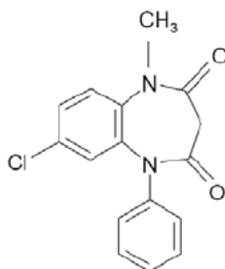
Chemical Names: 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4-(3*H*,5*H*)-dione

US Adopted Name (USAN): Clobazam

Laboratory Codes: A 50 376, HR 376, RU 4723

CAS : 22316-47-8

Chemical structure:



Chemical Formula: $C_{16}H_{13}ClN_2O_2$
Molecular Weight: 300.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED |
|---------|------|--------|-----------------|-------------------|--------------------------------------|---|
| (b) (4) | II | | (b) (4) | 1 | Adequate | 26-May-2011 (A. Khairuzzaman, Ph.D.) |
| | IV | | 3 | Adequate | 5/15/2008 Art Shaw, Ph.D. | |
| | III | | 4 | Adequate | - | |
| | III | | 4 | Adequate | See section P.2.4. in this review | |
| | III | | 4 | Adequate | - | |
| | III | | 4 | Adequate | See section P.2.4. in this review | |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|--|
| DMF | DMF # (b) (4) | Chemistry information for the Drug Substance, Clobazam |

18. STATUS:

| CONSULTS & CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|--------------------------------|--------------------------------------|------------|------------------------|
| EES | Pending | | |
| LNC | N/A | ---- | ---- |
| Methods Validation | Not Necessary | ---- | ---- |
| OSE-DMEPA | | ---- | ---- |
| Microbiology | Acceptable | 03/20/2012 | Steven P Donald |
| EA | Categorical Exclusion: Acceptable | 08/02/2012 | A. Khairuzzaman, Ph.D. |
| Biopharmaceutics | Dissolution: Acceptable | 10/01/2012 | A. Khairuzzaman, Ph.D. |

Executive Summary Section

The CMC and Biopharmaceutics Review for NDA 202-067

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (203-993) is **recommended for approval** from the perspective of chemistry, manufacturing, and controls and Biopharmaceutics. The Office of Compliance (OC) has given an acceptable recommendation for the manufacturing and testing facilities on 18th April, 2012.

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

There are no Phase 4 commitments.

II. Summary of CMC and Biopharmaceutics Assessments

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

Clobazam is a 1,5 benzodiazepine with anti-convulsant, sedative, anxiolytic and muscle relaxant properties. The drug product containing clobazam (Frisium) has been in the market worldwide (~80 countries including Canada and Mexico) since 1970's for the treatment of seizures associated with Lennox Gastaut syndrome (LGS) in patients 2 years or above.

ONFI (clobazam) Tablets received marketing approval in the United States on 21 October 2011 for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older. (NDA 202067). Since approval of NDA 202067 (Onfi Tablets), Lundbeck has developed a suspension formulation of clobazam targeted for LGS patients who have difficulty swallowing tablets. Since a suspension formulation is a new to-be-marketed dosage form of clobazam tablets, a single dose bioavailability study relative to the tablets was completed to support this application.

This review primarily captures the critical information pertaining to chemistry, manufacturing and control for the development of drug product, OnfiTM (clobazam) Suspension.

Executive Summary Section

Drug Substance

Clobazam is a 1,5 benzodiazepine with anticonvulsant, sedative, anxiolytic and muscle relaxant properties. All CMC related information for the drug substance, clobazam is referenced with DMF (b) (4) and has been found to be **adequate** by the reviewer, Dr. Akm Khairuzzaman.

Satisfactory batch analysis of several commercial scale batches has been provided. Up to 60 months of long term stability data, 6 months of accelerated stability data and photo stability data shows that the drug substance has acceptable stability profile.

Drug Product

The proposed drug product under this New Drug Application is an orally administered suspension preparation packed in a (b) (4) type III round amber glass bottle with a tamper-evident, child resistant screw cap closure filled with 120 mL of the suspension. Each 5 mL of this suspension preparation contains (b) (4) mg of clobazam. The suspension is berry flavored formulated with commonly used pharmaceutical grade excipients for suspension preparation. The excipients used are magnesium aluminum silicate, xanthan gum, citric acid monohydrate, disodium (b) (4) simethicone, polysorbate 80, methyl and propyl paraben, propylene glycol, mannitol solution, and berry flavor. All inactive ingredients except for the berry flavor are compendial.

The manufacturing process involves typical unit operations for suspension manufacture such as (b) (4). A risk assessment for the manufacture of this product was conducted to identify all input variables. Parameters evaluated were raw materials, manufacturing equipment, process steps and finished product testing. The severity of the product/process input parameters that could affect the product quality were evaluated using (b) (4) along with the (b) (4)

Based upon the risks identified and the mitigating actions (controls) in place for raw materials, equipment, processing and final finished product testing, consistent output of finished product of the required quality can be assured for every batch. The commercial product will be manufactured by the Rosemont Pharmaceuticals Ltd., located in West Yorkshire, UK.

Appropriate drug product specification is in place which includes: appearance, identification, assay, related substance, viscosity, particle size distribution, preservative assay, pH, microbial limits and dissolution. The limits proposed for all these test parameters were based on the clinical batches and were found to be reasonable by this reviewer.

The analytical methods to be used for the release of the finished products appears to be very straight forward. Clobazam identification, assay and related substances, and determination of methylparaben and propylparaben content are performed (b) (4)

Executive Summary Section

The applicant has manufactured three (3) registration stability batches and one (1) demonstration batch at the commercial manufacturing site (Rosemont Pharmaceuticals Ltd, UK). These batches were packed in a “to be marketed” container (b) (4) amber glass bottles with child resistant caps). Each batch size was (b) (4). Stability studies were conducted at 25 °C and 40 °C. Applicant will test at 30 °C storage condition if the product fails at 40 °C. A statistical analysis of the stability data was also conducted to propose a shelf life based on 12 months long term and 6 months accelerated data. The drug product has fairly acceptable stability specification in place. The test criteria include appearance, identification, assay, related substance, preservative assay, pH, density, viscosity and particle size distribution. Other types of stability studies on the product were also conducted. These studies includes: stress studies (multi pH, at 80 °C), temperature cycling study (-20°C for 2 days and then stored at 40°C for 2 days), and a photostability study. The 12 months long terms stability data and the 6 months accelerated stability data show that the drug product is chemically very stable. Applicant has proposed for a 24 months of product shelf life using statistical analysis of the available 12 months of data to support the 24 months of shelf life. Data shows that the product shelf life of 24 months can be granted from the chemical stability point of view. The drug product’s physical stability (phase separation upon storage and its redispersibility) has been found to be acceptable for 16 months (based on applicant’s visual confirmation of no sedimentation at the bottom of the bottle). There might be sedimentation after the 16 months and such sediments may not be redispersible readily upon shaking. However, if such physical instability occurs that is expected to be captured by the appearance and assay from stability test.

The Applicant has satisfactorily responded (on 30 August, 2012 and 27 September, 2012) to all the CMC and Biopharmaceutics deficiencies (further discussed in this review). Therefore, this NDA can be recommended for approval from Product Quality Perspective.

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

Onfi™ Suspensions is for oral administration in children ≥ 2 years-of-age and older for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome. The recommended target doses for children over 2 years of age and ≤ 30 kg body weight will initiate therapy at 5 mg QD and doses titrated at weekly intervals to a target dose of 10-20 mg/day. Patients >30 kg of body weight will initiate therapy at 10 mg daily.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (202-067) **can** be approved from the perspective of chemistry, manufacturing, and controls with 24 months of product shelf life.

The Applicant has satisfactorily responded (on 30 August, 2012 and 27 September, 2012) to all the CMC and Biopharmaceutics deficiencies (further discussed in this review).



PRODUCT QUALITY REVIEW
CMC and Biopharmaceutics



Executive Summary Section

III. Administrative

A. Reviewer's Signature

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

| | |
|------------------------------|--------------------------|
| Chemistry Reviewer: | Akm Khairuzzaman, Ph.D. |
| Biopharmaceutics Reviewer: | Akm Khairuzzaman, Ph.D. |
| Biopharmaceutics Team Leader | Angelica Dorantes, Ph.D. |
| CMC Lead: | Martha Heimann, Ph.D. |
| Branch Chief: | Ramesh Sood, Ph.D. |
| Project Manager: | Teshara Bouie |

C. CC Block, Rik Lostritto

Orig. NDA 202-993
HFD-120/Division File

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/s/

AKM KHAIRUZZAMAN

11/08/2012

Recommended for approval from CMC & Biopharmaceutics point of view

ANGELICA DORANTES

11/08/2012

RAMESH K SOOD

11/09/2012

MEMORANDUM



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

DATE: 11/07/2012

TO: Su-Lin Sun, CDER/OND/ODEI/DNP

FROM: Steven P. Donald, CDER/OPS/NDMS

THROUGH: Bryan Riley, CDER/OPS/NDMS

SUBJECT: NDA 203993 Onfi (clobazam) Oral Suspension proposed labeling change

The sponsor of NDA 203993 Onfi (clobazam) oral suspension has proposed a labeling change that may affect the stability of the drug product in the opened container. New language in the product insert includes “use up to 90 days” once the bottle has been opened, which is an increase from (b) (4). Product Quality Microbiology suggested the applicant provide stability data in a modified antimicrobial effectiveness test to support the increase in shelf life of the opened bottle as the current data from this test only support a 28 day open bottle shelf life. The sponsor responded with justification for the increased time and provided a stability study which assesses preservative levels over a period of 90 days in an opened bottle. Samples taken during this extended time met the acceptance criteria of 90% – 100% preservative level. This study was followed by antimicrobial effectiveness testing from the same opened bottle, according to USP<51>, with acceptable results over the 28 day period. The studies can be found in 3.2.P.2.6 in the 7/12/2012 submission to the application. This microbiology reviewer agrees with the sponsor’s justification and does not object to the proposed change in product labeling to increase the shelf life of the opened bottle to 90 days.

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/s/

STEVEN P DONALD
11/07/2012

BRYAN S RILEY
11/07/2012
I concur.

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

OND Division: Division of Neurology Products
NDA: 203-993
Applicant: Lundbeck, Inc.
Stamp Date: 28-Feb-2012
PDUFA Date: 28-Dec-2012
Trademark: Onfi®
Established Name: Clobazam
Dosage Form: Suspension
Route of Administration: Oral
Indication: Treatment of Lennox-Gastaut syndrome

CMC Lead: Martha R. Heimann, Ph.D.

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

Summary and Critical Issues:

Summary

Clobazam is a 1,5-benzodiazepine with sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. It is marketed in most of the world by Sanofi-aventis for the treatment of anxiety and epilepsy, but until recently it was not approved in the U.S. Onfi® (clobazam) Tablets were approved under NDA 202-067 on 21-Oct-2011 and are marketed by Lundbeck.

The current NDA provides for a 2.5 mg/mL oral suspension formulation of clobazam. The product is stated to be bioequivalent to the approved tablets; therefore, no clinical efficacy studies were performed. The product is intended for use in the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age. The recommended target doses are between 10 mg/day and 40 mg/day depending on age and body weight.

Drug Substance

CMC information for the drug substance is incorporated by cross-reference to Lundbeck's approved NDA 202-067 for Onfi® (clobazam) Tablets.

Drug Product

The proposed dosage form is a berry flavored oral suspension containing 2.5 mg/mL clobazam. The drug product will be packaged in a (b) (4) Type III, round, amber glass bottle with a tamper evident, child-resistant screw-cap closure. Each multi-dose bottle contains 120 mL of the suspension. The composition of Clobazam Oral Suspension is given in Applicant’s **Table 1** [Module 3.2.P.1] and reproduced below.

Table 1. Clobazam Oral Suspension Qualitative and Quantitative Composition

| Component | Quantity per mL | Function | Quality Standard |
|---|-----------------|----------------|------------------|
| Clobazam (b) (4) | 2.50 mg | Drug Substance | EP |
| Magnesium Aluminium Silicate (b) (4) | | | (b) (4) |
| Xanthan gum | | | |
| Citric Acid Monohydrate | | | |
| Disodium Hydrogen Phosphate Dihydrate | | | |
| Simethicone Emulsion (b) (4) | | | |
| Polysorbate 80 | | | |
| Methylparaben | | | |
| Propylparaben | | | |
| Propylene Glycol | | | |
| Sucralose | | | |
| Maltitol Solution | | | |
| Berry flavor | | | |
| Citric Acid Monohydrate (b) (4) | | | |
| Disodium Hydrogen Phosphate Dihydrate (b) (4) | | | |
| Purified Water (b) (4) | | | |

All inactive ingredients except the berry flavor are compendial and are commonly used as excipients in oral dosage forms. The composition of the berry flavor is given in the manufacturer’s DMF (b) (4)

The NDA includes a very minimal Pharmaceutical Development section, with information presented as brief narratives. A risk assessment for the manufacturing process is provided as an attachment to Module 3.2.P.3.4.

Clobazam Oral Suspension will be manufactured by Rosemont Pharmaceuticals, Leeds, West Yorkshire, UK. The manufacturing process is outlined in the applicant’s Figure 1 [Module 3.2.P.3.3]. The manufacturing process involves typical unit operations for an oral suspension, including, (b) (4).

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been assigned as the CMC and Biopharmaceutics reviewer. The drug substance is not a new molecular entity; therefore, a Division-level regulatory briefing is not indicated.

Martha R. Heimann, Ph.D.
CMC Lead

Date

Ramesh Sood, Ph.D.
Branch Chief

Date

ATTACHMENT 1

Manufacturing Establishments for Onfi® (clobazam) Oral Suspension

Drug substance manufacturer:

| | |
|---------------------------------|--|
| Manufacturer: |  (b) (4) |
| Address: | |
| Responsibilities: | |
| FDA Registration Number: | |
| Contact | |

Drug product manufacturer:

Table 1. Manufacturing, Packaging and Testing Facilities

| | |
|---|---|
| Manufacturer: Address: |  (b) (4) |
| Responsibility: | |
| Facility Establishment Identifier: | |
| Contact | |
| | |

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

| | | |
|-------------------------------------|---|---|
| NDA Number: 203-993 | Supplement Number and Type: N/A | Established/Proper Name: Clobazam Oral Suspension |
| Applicant: Lundbeck, Inc. | Letter Date: 28-Feb-2012 | Stamp Date: 28-Feb-2012 |

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

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

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

NDA 203-993 Filing Checklist

| | | | | |
|-----|--|-----|--|--|
| 8. | <p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | X | | Revised form 356h requested by ONDQA PM. |
| 9. | <p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | N/A | | No additional facilities proposed. |
| 10. | <p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p> | X | | |

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

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

NDA 203-993 Filing Checklist

| D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API) | | | | |
|--|---|------------|-----------|--|
| | Parameter | Yes | No | Comment |
| 12. | Does the section contain a description of the DS manufacturing process? | X | | Cross-referenced to approved NDA 202067. |
| 13. | Does the section contain identification and controls of critical steps and intermediates of the DS? | X | | Cross-referenced to approved NDA 202067. |
| 14. | Does the section contain information regarding the characterization of the DS? | X | | Cross-referenced to approved NDA 202067. |
| 15. | Does the section contain controls for the DS? | X | | Cross-referenced to approved NDA 202067. |
| 16. | Has stability data and analysis been provided for the drug substance? | X | | Cross-referenced to approved NDA 202067. |
| 17. | Does the application contain Quality by Design (QbD) information regarding the DS? | | X | |
| 18. | Does the application contain Process Analytical Technology (PAT) information regarding the DS? | | X | |

NDA 203-993 Filing Checklist

| E. DRUG PRODUCT (DP) | | | | |
|-----------------------------|---|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 19. | Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging? | X | | |
| 20. | Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable? | X | | |
| 21. | Is there a batch production record and a proposed master batch record? | X | | |
| 22. | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product? | N/A | | Proposed commercial formulation was used in bioequivalence study with approved Onfi® (clobazam) Oral Tablets, 20 mg. |
| 23. | Have any biowaivers been requested? | X | | In Module 1.12.14, the applicant requests a biowaiver waiver from conducting in vivo bioavailability studies comparing the proposed oral suspension to the 5 and 10 mg approved tablets. It is unclear whether such a biowaiver is needed and this issue is deferred to the reviewer. |
| 24. | Does the section contain description of to-be-marketed container/closure system and presentations)? | X | | |
| 25. | Does the section contain controls of the final drug product? | X | | |
| 26. | Has stability data and analysis been provided to support the requested expiration date? | X | | Limited data (6 months long-term and accelerated) are provided in initial NDA. |
| 27. | Does the application contain Quality by Design (QbD) information regarding the DP? | | X | |
| 28. | Does the application contain Process Analytical Technology (PAT) information regarding the DP? | | X | |

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

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

NDA 203-993 Filing Checklist

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

| DMF # (b) (4) | TYPE | HOLDER | ITEM REFERENCED | LOA DATE | COMMENTS |
|------------------|------|--------|-----------------|-------------|----------|
| | IV | | (b) (4) | 16-Sep-2011 | |
| | III | | | 16-Sep-2011 | |
| | III | | | 23-Jan-2012 | |
| | III | | | 29-Sep-2011 | |
| | III | | | 29-Sep-2011 | |

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

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

{See appended electronic signature page}

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

{See appended electronic signature page}

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

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

/s/

MARTHA R HEIMANN
04/23/2012

RAMESH K SOOD
04/23/2012