

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202067Orig1s000**

**CHEMISTRY REVIEW(S)**

**ONDQA Division Director's Memo**  
**NDA 202067, ONFI (clobazam) Tablets 5 mg, 10 mg, and 20 mg**  
**Date: 21-OCT-2011**

**Introduction**

Clobazam is a member of the benzodiazepine class. Although marketed elsewhere in the world since the 1970's this is its introduction into the U.S. ONFI (clobazam) tablets are indicated for the treatment of seizures associated with Lennox-Gastaut syndrome. The recommended target for children over 2 years of age and  $\leq 30$  kg body weight is to initiate therapy at 5 mg daily and then titrate the dose at weekly intervals up to a target dose of 10-20 mg/day. Patients  $>30$  kg of body weight will initiate therapy at 10 mg daily.

**Administrative**

Supported by ten DMFs, this original 505(b)(1)NDA was received 23-DEC-2010 from Lundbeck, Inc. of Deerfield IL and was given standard review status. A CMC amendment received 21-JUN-2011 was also reviewed. An EES finding of "overall acceptable" is dated 12-OCT-2011.

**ONDQA recommends approval from the CMC perspective.**

**Drug Substance: clobazam**

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

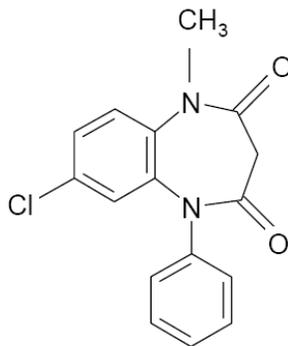
Chemical Formula:  $C_{16}H_{13}ClN_2O_2$

US Adopted Name (USAN): Clobazam

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

CAS : 22316-47-8

Chemical structure:



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 an acceptable stability profile.

**Drug Product: ONFI Tablets 5 mg, 10 mg, and 20 mg.**

ONFI tablets are (b) (4)  
Each tablet is white, round, and debossed with “LU” on one side and “5”, “10” or “20” on the other side.

The drug product is formulated using conventional excipients: lactose monohydrate, corn starch, silicon dioxide, magnesium stearate and talc.

Onfi (all strengths: 5 mg, 10 mg and 20 mg) tablets are supplied in 40 cc HDPE bottles with an induction seal, child resistant (CR) cap, and (b) (4)  
(b) (4) Each bottle will contain 100 tablets.

Stability studies were conducted on nine batches (three batches for each strength) manufactured at the proposed commercial manufacturing site, Catalent Pharma Solutions (Catalent), in Winchester, Kentucky.

Upon review of all these data and the statistical extrapolation of the data, it was decided to approve 36 months of drug product shelf life for all the strength of Onfi (clobazam) tablets.

**CONVEY THE COMMENT BELOW TO APPLICANT IN ACTION LETTER:**

**A shelf-life of 36 months at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [USP Controlled Room temperature] is approved.**

Thank you.

Rik Lostritto, Ph.D., Director, ONDQA Division I.

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/s/  
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RICHARD T LOSTRITTO  
10/21/2011

**CMC Memo to File**

To:	NDA
Date	17 Oct 2011
Sponsor:	Lundbeck Inc.
Drug:	Onfi™ (clobazam) Tablets
Subject	Approval recommendation
Reviewer	Dr. Akm Khairuzzaman

Pursuant the overall “acceptable” recommendation given on 12-Oct-2011 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 202-067 be approved.

HFD-/Division File  
HFD-120

\_\_\_\_\_  
Akm Khairuzzaman, Ph.D.  
Chemistry Reviewer

\_\_\_\_\_  
Ramesh Sood, Ph.D.  
Branch Chief, ONDQA

**Attachment**

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

<b>Application:</b>	NDA 202067/000	<b>Sponsor:</b>	LUNDBECK H
<b>Org. Code:</b>	120		4 PKY NORTH
<b>Priority:</b>	1		DEERFIELD, IL 60015
<b>Stamp Date:</b>	23-DEC-2010	<b>Brand Name:</b>	CLOBAZAM
<b>PDUFA Date:</b>	23-OCT-2011	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	CLOBAZAM
<b>District Goal:</b>	24-AUG-2011	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
			001; TABLET; CLOBAZAM; 5MG
			002; TABLET; CLOBAZAM; 10MG
			003; TABLET; CLOBAZAM; 20MG
<b>FDA Contacts:</b>	T. BOUIE	Project Manager	301-796-1649
	A. KHAIRUZZAMAN	Review Chemist	(HFD-800) 301-796-3886
	M. HEIMANN	Team Leader	301-796-1678

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**Overall Recommendation:**            ACCEPTABLE            on 12-OCT-2011    by D. SMITH            ( )

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/s/  
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AKM KHAIRUZZAMAN

10/17/2011

NDA-202067 can be approved from CMC point of view

RAMESH K SOOD

10/18/2011

## **NDA 202-067**

**Onfi<sup>TM</sup> (clobazam) Tablets,  
5 mg, 10 mg & 20 mg**

**Lundbeck Inc.**

**Akm Khairuzzaman, Ph.D.  
ONDQA/DNDQA1/Branch 1**

**Reviewed for the Division of Neurology Products, HFD-120**

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# Chemistry Review Data Sheet

1. NDA 202-067
2. REVIEW #: 1
3. REVIEW DATE: 07/27/2011  
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	23-December-2010
CMC amendment	21 June 2011

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	Onfi™
<b>Non-Proprietary Name (USAN)</b>	Clobazam
<b>Code Names</b>	N/A
<b>Chemistry Type</b>	5

## Chemistry Review Data Sheet

Submission Priority	S
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9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Benzodiazepine.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 5 mg, 10 mg & 20 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:   X   Rx        OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

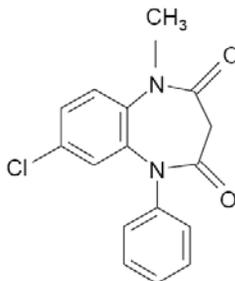
       SPOTS product – Form Completed

  X   Not a SPOTS product

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

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:  $C_{16}H_{13}ClN_2O_2$

Chemistry Review Data Sheet

Molecular Weight: 300.7

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Clobazam		In Adequate	14-Mar-2011 (A. Khairuzzaman, Ph.D.)
	III		(b) (4)	4	Adequate	N/A
	III			4	Adequate	07-Jul-2010 (Caroline Strasinger)
	III			4	Adequate	-
	III			4	Adequate	-
	III			4	Adequate	-
	III			4	Adequate	-
	III			4	Adequate	-
	III			4	Adequate	13-Jan-2010 (George Lunn)

<sup>1</sup> Action codes for DMF Table:  
1 – DMF Reviewed.

## Chemistry Review Data Sheet

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
DMF	[REDACTED] (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		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman, Ph.D.
Biopharmaceutics	Dissolution methods & limit: Acceptable	08/01/2011	A. Khairuzzaman, Ph.D.

# The Chemistry Review for NDA 202-067

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (202-067) cannot be recommended for approval from the perspective of chemistry, manufacturing, and controls because the Office of Compliance (OC) has not yet given an acceptable recommendation for the manufacturing and testing facilities.

#### 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 Chemistry 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.

Clobazam has never been marketed in US. It has got orphan drug designation on 18<sup>th</sup> December 2007 for the treatment of LGS. This NDA was submitted under the 505(b)(1) in accordance with 21 CFR 314.50.

This review primarily captured the critical information pertaining to chemistry, manufacturing and control for the development of drug product, Onfi™ (clobazam) Tablets, 5 mg, 10 mg and 20 mg.

#### 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.

## Executive Summary Section

Drug Product

The proposed drug product under this New Drug Application is an orally administered tablet with strengths: 5mg, 10 mg and 20 mg. The trade name proposed is Onfi™. It has been mentioned earlier that the drug product containing clobazam (named as 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.

Clobazam is an (b) (4) immediate release tablets (b) (4) that will contain 5 mg, 10 mg and 20 mg of clobazam per tablet by using (b) (4) (b) (4). Each tablet is white, round, and debossed with "LU" on one side and "5", "10" or "20" on the other side.

The drug product is formulated using commonly used pharmaceutical grade excipients such as lactose monohydrate, corn starch, silicon dioxide, magnesium stearate and talc. (b) (4)

(b) (4) The excipients are sourced from vendors that have been appropriately qualified according to Catalent's (drug product manufacturer) vendor qualification program. No non-compendial ingredients are used in the manufacture of clobazam tablets. A different formulation composition for the 5 mg tablets were used at phase two stage. (b) (4) (b) (4). However, both formulation were tested for bioequivalence study and were found to be equivalent.

The original development of Frisium® (clobazam) 10 mg tablets was conducted by Sanofi-Aventis legacy company. The sponsor for this NDA, Lundback purchased the rights to develop and market this product under the trade name of Onfi in United States. Onfi will be manufactured by Catalant Pharma in Kentucky and distributed by (b) (4) (b) (4)

(b) (4) The manufacturing process (b) (4) (b) (4)

The applicant has manufactured nine (9) registration batches. The batch size of the final blend was sufficient for making (b) (4) tablets of the 5 mg strength; (b) (4) tablets of the 10 mg strength; and (b) (4) of the 20 mg strength.

## Executive Summary Section

The drug product has fairly acceptable specification in place. The test criteria include appearance, identification, related substance, content uniformity, assay, dissolution and microbiological limits. It is to be noted that active drug component (clobazam) has European monograph that includes the known impurities by their name. Appropriate analytical methods are in place for the drug product release tests. These analytical methods were validated as per the ICH Q2 requirement. Detailed batch analysis data for all the registration batches were provided. Upon review of these data it was found that all batches met the acceptance criteria and very minimal batch to batch variability was observed.

Onfi (all strengths: 5 mg, 10 mg and 20 mg) will be supplied in a 40 cc HDPE bottle with an induction seal, child resistant (CR) cap, and [REDACTED]<sup>(b) (4)</sup>. Each bottle will contain 100 tablets.

The stability studies were conducted on nine (9) registration batches (three batches for each strength) manufactured at the proposed commercial manufacturing site, Catalent Pharma Solutions (Catalent), in Winchester, Kentucky. All batches were packed in the proposed commercial packaging. A maximum of 36 months of stability data under the long term condition and 6 months of stability data under accelerated condition were provided in the application with a post approval stability protocol and commitment. Appropriate statistical analysis was also conducted on the stability data. Upon review of all these data and the statistical extrapolation of the data, it was decided to approve 36 months of product shelf life for all the strength of Onfi (clobazam) tablets.

At this stage of this NDA review, the overall recommendation from compliance on all the facility is still pending. Few CMC deficiencies were sent out to the sponsor and all of them are addressed by the sponsor satisfactorily. Currently there are no pending CMC issues and therefore this NDA can be approved from CMC point of view.

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

Onfi™ Tablets is for oral administration in children  $\geq 2$  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  $\leq 30$  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.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

/s/ A. Khairuzzaman, Ph.D.

**B. Endorsement Block**

Chemistry Reviewer:	Akm Khairuzzaman, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heiman, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Teshara Bouie

**C. CC Block**

Orig. NDA 202-067  
HFD-120/Division File

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/s/  
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AKM KHAIRUZZAMAN

08/02/2011

This NDA cannot be approved from CMC point of view due to pending OC recommendation

RAMESH K SOOD

08/02/2011

Initial Quality Assessment  
Branch I  
Pre-Marketing Assessment Division I

**OND Division:** Division of Neurology Products  
**NDA:** 202-067  
**Applicant:** Lundbeck, Inc.  
**Stamp Date:** 23-Dec-2010  
**PDUFA Date:** 23-Oct-2011  
**Trademark:** Onfi®  
**Established Name:** Clobazam  
**Dosage Form:** Tablet  
**Route of Administration:** Oral  
**Indication:** Treatment of Lennox-Gastaut syndrome  
  
**CMC Lead:** Martha R. Heimann, Ph.D.

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

## Summary and Critical Issues:

### *Summary*

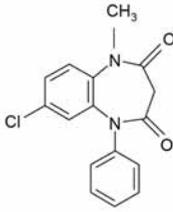
Clobazam is a 1,5-benzodiazepine with sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. It is marketed in most of the world by Sanofi-aventis under the tradename Frisium® for the treatment of anxiety and epilepsy; but it is not approved in the U.S. In 2004, Ovation Pharmaceuticals obtained marketing rights for clobazam in the US, Canada, and Mexico from Sanofi-aventis. Ovation initiated development of clobazam for treatment of Lennox-Gastaut syndrome in 2005 under IND 70,125. Ovation was subsequently acquired by Lundbeck.

The current NDA provides for an immediate release clobazam tablet formulation to be available in three strengths, 5 mg, 10 mg, and 20 mg. The product is intended for use in the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children  $\geq 2$  years of age. The recommended target doses, depending on age and body weight, are between 10 mg/day and 40 mg/day given in two divided doses. The product may be administered by crushing and mixing with applesauce.

### Drug Substance

The active ingredient in Onfi® Tablets is clobazam (chemical name: 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4-(3H,5H)-dione). It is a well characterized small molecule with molecular formula  $C_{16}H_{13}ClN_2O_2$  and molecular weight 300.7. Clobazam is described in the European Pharmacopeia (EP) but not the USP.

The chemical structure of clobazam is:



The bulk drug substance (b) (4) which is cross-referenced for CMC information. The DMF appears complete enough to allow for a substantive review but it has not been reviewed previously. Limited manufacturing and control information is provided in the NDA itself.

(b) (4) (b) (4)  
(b) (4)

(b) (4) (b) (4)

The specification for clobazam is given in the Applicant's **Table 1 Specification of Clobazam, Micronized Drug Substance**, which is reproduced below. Analytical procedures and methods validation are referenced to DMF (b)(4) and not provided in the application.

**Table 1 Specification for Clobazam, (b)(4) Drug Substance**

Test Item	Method	Acceptance Criteria
Appearance	Ph. Eur.	White or almost white, crystalline powder
Identification		
- IR Spectrum	Ph. Eur.	Corresponds (reference spectrum)
- LC	SADG <sup>1</sup>	Corresponds
- Melting Point	SADG <sup>1</sup>	182°C to 185°C
Appearance of Solution	SADG <sup>1</sup>	Clear and colorless
Related Substances (b)(4)		(b)(4)
- Impurity A	Ph. Eur.	(b)(4)
- Any other impurity (b)(4)	Ph. Eur.	
- Unspecified impurities	Ph. Eur.	
- Total impurities (other than impurity A)	Ph. Eur.	
Sulphated Ash	Ph. Eur.	
Heavy Metals	SADG <sup>1</sup>	
(b)(4)	Ph. Eur.	
Assay (UV)	Ph. Eur.	97.0 to 103.0% calculated with reference to the (b)(4)
Particle Size (b)(4)	SADG <sup>1</sup>	(b)(4)

<sup>1</sup> SADG = Sanofi-Aventis Deutschland GmbH internal test method.

(b)(4)

(b)(4)

Drug Product

The proposed dosage form is an (b)(4) immediate release tablet containing 5 mg, 10 mg, or 20 mg of clobazam. Tablets are debossed on one side with the letters "LU" and on the other side with the numbers 5, 10 or 20 as appropriate to the tablet strength. The applicant does not specify

tablet size, shape, or color in the description and composition section; however, per the drug product specification the tablets are white. (b) (4)

The components and composition of Onfi® Tablets are summarized in the applicant's **Table 1, Quantitative Composition of Clobazam Tablets**, which is shown below.

**Table 1. Quantitative Composition of Clobazam Tablets**

(b) (4)	Theoretical Quantity			Function	Quality Standard
	(mg/tablet)				
Clobazam, (b) (4)	(b) (4)			Drug Substance (b) (4)	EP
Corn Starch	(b) (4)				NF
Lactose Monohydrate	(b) (4)				NF
Corn Starch	(b) (4)				NF
(b) (4)	(b) (4)				USP
Magnesium Stearate	(b) (4)				NF
Talc	(b) (4)				USP
Silicon Dioxide	(b) (4)				NF
Total Tablet Weight:		60.0	120.0	240.0	
(b) (4)					

Tablet components are commonly used as excipients in solid oral dosage forms. All components comply with compendial (USP/NF) requirements.

Onfi® (clobazam) Tablets will be packaged in 100-count, 40 cc HDPE bottles with (b) (4) CR closures, aluminum foil induction seal and (b) (4)

The proposed commercial formulation of Onfi® Tablets (b) (4). During development, however, the applicant used a second tablet formulation for Phase 2 studies. The Phase 2 product was manufactured by (b) (4). Phase 2 tablets were qualitatively and quantitatively different from the commercial formulation and were manufactured (b) (4). The compositions of the clinical formulations are compared in Applicant's **Table 1. Clobazam Formulations Used in Clinical Trials**, which is reproduced on the following page. Note that only 5 mg tablets of Phase 2 and Phase 3 (commercial) formulation were used in controlled studies (OV-1002 and OV-1012). The Phase 2 5 mg tablets and all strengths of the Phase 3 formulation were used in an open label study (OV-1004). The applicant states that Phase 2 and Phase 3 5 mg tablets are bioequivalent (Study OV-1016). (b) (4)

**Table 1. Clobazam Formulations Used in Clinical Trials**

Ingredient	(b) (4) (Phase 2)		Catalent (Phase 3)		
	Amount, %	Amount, mg/tablet	Ingredient	Amount, %	Amount, mg/tablet <sup>2</sup>
Clobazam	(b) (4)	5.00	Clobazam	(b) (4)	5.00
Lactose, (b) (4) NF	(b) (4)	(b) (4)	Lactose monohydrate, NF/EP	(b) (4)	(b) (4)
Starch (corn) NF	(b) (4)	(b) (4)	Corn starch, NF/EP	(b) (4)	(b) (4)
(b) (4) NF	(b) (4)	(b) (4)	---	(b) (4)	(b) (4)
(b) (4) silicon dioxide, NF	(b) (4)	(b) (4)	Silicon Dioxide, NF	(b) (4)	(b) (4)
Magnesium Stearate, NF	(b) (4)	(b) (4)	Magnesium Stearate, NF/EP	(b) (4)	(b) (4)
Talc, USP	(b) (4)	(b) (4)	Talc, USP/EP	(b) (4)	(b) (4)
Total	100%	60.00		100%	60.00

<sup>1</sup> (b) (4)

<sup>2</sup> Amount shown in this table is for the 5 mg tablet. (b) (4)

With respect to pharmaceutical development, no formulation development or manufacturing development information is provided in the NDA. (b) (4)

Onfi® (clobazam) Tablets will be manufactured by Catalent Pharma Solutions in Winchester, Kentucky. (b) (4)

The proposed regulatory specifications for Onfi® Tablets are shown on the following page (applicant's **Table 1. Clobazam Tablets Proposed Specifications**). The proposed analytical procedures appear straight-forward. Clobazam Assay, Related substances, and Content uniformity are determined using a single reverse phase HPLC method (b) (4)

(b) (4) Dissolution is determined using USP (b) (4). Dissolution results are quantitated using a shortened version of the HPLC method used for assay, related substances and content uniformity.

**Table 1. Clobazam Tablets Proposed Specifications**

Test Items	Methods	Current Proposed Acceptance Criteria
Appearance	Visual	White tablet, debossed on one side with "LU" and the tablet dose <sup>1</sup> on the other side.
Identification <sup>2</sup>	IR	Conforms to reference spectrum
Identification <sup>2</sup>	HPLC	Conforms to reference standard retention time
Assay	HPLC	90.0 - 110.0% Label Claim
Related Substances	HPLC	Individual impurity: NMT (b) (4) Total impurities: NMT (b) (4)
Uniformity of Dosage Units <sup>2</sup> (Content Uniformity)	HPLC and USP <905>	Conforms to current USP
Dissolution	HPLC	Q = (b) (4) For S1, 6 of 6 tablets NLT (b) (4) minutes. S2 and S3 as per USP.
Microbial Limits	USP <61> and <62>	(b) (4)

<sup>1</sup> "5" for 5 mg tablet, "10" for 10 mg tablet, and "20" for 20 mg tablet.

<sup>2</sup> These tests are run for batch release only.

The NDA stability package includes long-term stability data through 18 – 36 months, and accelerated data through 6 months for three batches per tablet strength. Batch scales for stability batches ranged from pilot (b) (4). The applicant indicates that all batches were manufactured (b) (4)

All batches were manufactured at the proposed commercial facility. The applicant proposes a 36-month shelf life. Based on the batch scales for the primary stability batches, (b) (4)

Based on the use of a (b) (4), the applicant also proposes (b) (4)

The acceptability of the proposed 36 month expiry, and of the reduced testing post-approval and annual batch stability commitments, is deferred to the primary reviewer.

**Critical issues for review**

*Drug Substance:*

(b) (4)

(b) (4)

No information regarding solid state characteristics of clobazam (e.g., polymorphism) was provided in the NDA itself. The reviewer should ensure that this is adequately addressed in the DMF.

*Drug Product:*

The lack of any information related to formulation and process development is noted. It is also noted that the manufacturing process description provided by the applicant is abbreviated and lacking in detail. Further, the applicant has not provided data to support the proposed manufacturing conditions or process controls.

### **Additional issues**

*Administrative:* The firm has submitted a claim for categorical exclusion under 25.31(b). Use of this product is not expected to cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

*Establishment Evaluation:* All facilities identified in the NDA were submitted in EES on 12-Jan-2011.

*Labeling/Established Name:* The active ingredient in Onfi® Tablets, clobazam, is a neutral molecule. Therefore, there is no issue of consistency between the established name (clobazam tablets) and the labeled potency.

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

With regard to the description and composition of the drug product (Module 3.2.P.1) provide a comprehensive description of tablet appearance including shape (e.g., round, oblong, flat, beveled, etc.) and approximate dimensions. Similarly, revise the drug product appearance criteria in Module 3.2.P.5 to include tablet shape and size.

In Module 3.2.P.3 you have provided only a brief description of the manufacturing process. In accordance with 21 CFR § 314.50(d)(1)(ii)(c), provide copies off the proposed or actual master production record, including a description of the equipment, to be used for manufacture of a commercial lot of the drug product or a comparably detailed description of the production process.

With regard to manufacture of clobazam tablets, you have not provided data from development or engineering studies to support the proposed process control parameters and acceptance criteria. Provide justification for designation of <sup>(b)(4)</sup> [REDACTED]

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

The NDA is fileable from a CMC perspective.

The drug substance is a well-defined small molecule, the tablet formulation is relatively simple, and there are no QbD aspects to the submission. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The Biopharmaceutics aspects of the submission have been assigned to Akm Khairuzzaman.

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

\_\_\_\_\_  
Date

Ramesh Sood, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

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

**NDA Numbers: 202-067**

**Applicant: Lundbeck, Inc.**

**Stamp Date: 23-Dec-2011**

**Drug Name: Clobazam Tablets**

**NDA Type: Standard**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		Cross-referenced to DMF (b) (4)
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	NA		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA

Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARTHA R HEIMANN  
01/14/2011

RAMESH K SOOD  
01/14/2011