

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204370Orig1Orig2s000

CHEMISTRY REVIEW(S)

OPQ Recommendation: Approval.

NDA 204370

Vraylar (cariprazine) capsules

Review #3

(Includes updated executive summary (p.2), labeling evaluation (p.4) and facilities evaluation (p.5))

Drug Name/Dosage Form	Cariprazine capsules
Strength	1.5 mg, 3.0 mg, 4.5mg, & 6.0 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Forest Laboratories
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	17 DEC 2015	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sherita McLamore	Branch I/DNDP I
Drug Product		
Process		
Microbiology		
Facility	Zhong Li	OPF
Biopharmaceutics	n/a	
Regulatory Business Process Manager	Dahlia A. Woody	OPRO
Application Technical Lead	David Claffey	Branch I/DNDP I
Laboratory (OTR)	n/a	
ORA Lead	n/a	
Environmental Assessment (EA)	n/a	

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: Recommend approval.

In the first review cycle an approval recommendation was made from a CMC perspective. No new CMC information was provided in this review cycle, however the facility recommendation required reevaluation and was found to be adequate. The labeling was also found to be adequate.

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

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance, cariprazine hydrochloride, is a new molecular entity. It is a non-hygroscopic white to off-white (b)(4) solid with molecular weight of 463.87. (b)(4)

The drug substance synthesis and controls were described in DMF 26321. The DMF was found to be adequate to support this application. Drug substance quality is ensured through in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, assay, impurities, particle size distribution, residual solvents, heavy metals and (b)(4). The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance was demonstrated through appropriate stability studies to support a retest period of (b)(4) months.

B. Drug Product [Established Name] Quality Summary

Vraylar (cariprazine) capsules is an immediate release product to be marketed in (b)(4) strengths (1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, (b)(4)). The labeled strength is based on cariprazine free base. The drug product formulation uses standard compendial excipients with all capsules having the same fill weight. (b)(4)

The manufacturing process includes (b)(4)

The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through release testing. The drug product specification includes testing for description, identification, assay, content uniformity, (b)(4), dissolution, microbial purity and degradation products. The analytical procedures for the drug product are adequately described and validated. The provided stability data support a 24-month expiration period for this product. The drug product is stored at 20 - 25°C with excursions permitted 15-30°C (59-86°F).

Additionally, the applicant has proposed a comparability protocol to qualify an alternate site for the drug substance manufacturing. The protocol was reviewed and found to be acceptable.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Vraylar
Non Proprietary Name of the Drug Product	Cariprazine capsules
Non Proprietary Name of the Drug Substance	
Proposed Indication(s) including Intended Patient Population	For the treatment of schizophrenia and the treatment of manic episodes associated with bipolar 1 disorder

Primary Quality Review

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

At the end of the first review cycle, the application was recommended for approval from a CMC perspective. Accordingly, there were no CMC comments included in the agency's November 19, 2013 Complete Response Letter (CRL) and no updated CMC information included in the applicant December 17, 2014 response.

Labeling

The package insert and labeling was review in conjunction with the response to agency's November 19, 2013 CRL. The labeling was updated as previously requested in the Agency's June 5, 2013 Information Request Letter to have the established name consistent with the strength and to include the protect from light statement for the 3.0 and 4.5 mg capsules. The new label and package insert also includes the Tradename, Vralylar (see representative label below). There were no other changes noted it the "Description" "Dosage Form and Strengths" or "How Supplied" sections.



OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature: Adequate

Sherita D. Mclamore -A

Digitally signed by Sherita D. Mclamore -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300148713, cn=Sherita D. Mclamore -A
Date: 2015.05.20 10:00:11 -04'00'

Secondary Review Comments and Concurrence:

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
 Date: 2015.05.20 09:24:24 -04'00'

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
CHEMICAL WORKS OF GEDEON RICHTER PLC	3002806762	CSN – Manufacturing, packaging, release and stability testing of drug substance	None	PAI waived because of site history and low risk processes	Acceptable Based on Profile

Reviewer’s Assessment:

CHEMICAL WORKS OF GEDEON RICHTER PLC. (FEI 3002806762)

The site is responsible for manufacturing, packaging, release and stability testing of drug substance. The facility was last inspected 5/2013 (NAI) and was found to be acceptable for the chemical synthesis operations.. N204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Forest Laboratories Ireland, Ltd.	3002806993	CHG - Drug product manufacturing, release and stability testing	None	PAI waived because of site history and low risk processes	Acceptable Based on DO Recommendation
FOREST RESEARCH INSTITUTE INC	1000521508	CTL - Drug product release and stability testing	None	PAI waived because of site history and low risk processes	Acceptable Based on Profile
	(b) (4)	CTL - Microbiological testing	None	PAI waived because of site history and low risk processes	Acceptable Based on Profile
		CTL - Microbiological testing	None	PAI waived because of site history and low risk processes	Acceptable Based on Profile
Forest Pharmaceuticals, Inc.	1523957	CHG - Drug product packaging (bottle & blister)	None	PAI waived because of site history and low risk processes	Acceptable Based on Profile
	(b) (4)	CHG - Drug product packaging (bottle & blister)	None	PAI waived because of site history and low risk processes	Acceptable Based on DO Recommendation

Reviewer's Assessment:

Forest Laboratories Ireland, Ltd. (FEI 3002806993)

This site is responsible for drug product manufacturing, release and stability testing. The facility was last inspected 2/2015 (NAI). A district file review was requested and conducted; and the facility was found to be acceptable for the proposed operations. NDA204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

FOREST RESEARCH INSTITUTE INC (FEI 1000521508)

This site is responsible for drug product release and stability testing. The facility was last inspected 1/2014 (NAI) and was found to be acceptable for the proposed operations. NDA204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

(b) (4)

This site is responsible for drug product microbiological testing. The facility was last inspected (b) (4) (NAI) and was found to be acceptable for the proposed operations. NDA204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

(b) (4)

The site is responsible for drug product microbiological testing. The facility was last inspected (b) (4) (NAI) and was found to be acceptable for the proposed testing operations. NDA204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

Forest Pharmaceuticals, Inc. (FEI 1523957)

The site is responsible for drug product packaging (bottle & blister). The facility was last inspected 11/2012 (VAI) and was found to be acceptable for the proposed packaging operations. NDA204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

(b) (4)

The site is responsible for drug product packaging (bottle & blister). The facility was last inspected (b) (4) (NAI). A district file review was requested and conducted; and the facility was found to be acceptable for the proposed operations. NDA204370 pre-approval coverage is not required. **This facility is acceptable based on previous inspectional history.**

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on firm inspectional history, the manufacturing facilities as listed above for NDA 204370 are found to be acceptable.

Zhong Li, Ph.D.
Chemist, OPQ/OPF/DIA/IABI

Zhong Li -S

Digitally signed by Zhong Li -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhong Li -S, 0.9.2342.19200300.100.1.1=2000695751
Date: 2015.05.19 18:19:57 -04'00'

Secondary Review Comments and Concurrence:

I concur with this Facility Assessment

Zhihao Peter Qiu, Ph.D.
Branch Chief, OPQ/OPF/DIA/IABI

**Zhihao
Qiu -S**

Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274
Date: 2015.05.20 08:04:14 -04'00'

APPLICATION TECHNICAL LEAD SIGNATURE:

David J.
Claffey -S

Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300225
565, cn=David J. Claffey -S
Date: 2015.05.19 16:49:16 -04'00'

NDA 204-370**Cariprazine HCl Capsules****1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg**

(b) (4)

Forest Laboratories, Inc**Sherita D. McLamore-Hines, Ph.D.**Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA: 204-370
2. REVIEW: #2
3. REVIEW DATE: October 29, 2013
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	November 19, 2012
Amendment	December 13, 2012
Amendment	April 8, 2013
Amendment	February 26, 2013
Amendment	February 8, 2013
Amendment	June 14, 2013
Amendment	July 9, 2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Amendment

Document Date
October 25, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:

Forest Laboratories, Inc

Chemistry Review Data Sheet

Address: Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Representative: n/a

Telephone: 201.427.8326

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name (USAN): Cariprazine HCl
- c) Code Name/# (ONDC only): RGH-188
- d) Chem. Type/Submission
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Schizophrenia and Treatment of Manic Episodes Associated with Bipolar I Disorder

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, (b) (4)

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

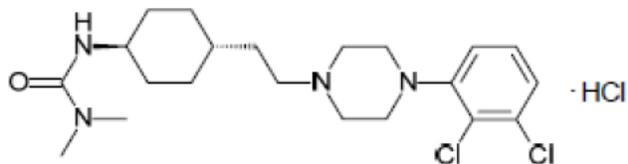
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: *trans*-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl-N',N'-dimethylurea hydrochloride

Chemistry Review Data Sheet

Molecular Formula: $C_{21}H_{32}Cl_2N_4O \cdot HCl$

Molecular Weight: 463.87



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
26321	II	Geodeon Richter Plc	Drug Substance	1	Adequate	6/28/2013	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

Chemistry Review Data Sheet

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	26321	Synthesis of the drug substance

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	10/07/2013	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	Acceptable	07/16.2013	Sandra Suarez
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	8/14/2013	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) <i>Acceptable</i>	07/11/2013	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	

Executive Summary Section

The Chemistry Review for NDA 204-370**The Executive Summary****A. Recommendation and Conclusion on Approvability**

This application is recommended for approval from a CMC perspective.

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

There are no CMC Phase 4 activity recommendations.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Cariprazine Hydrochloride is the active pharmaceutical ingredient in this application. Cariprazine Hydrochloride is a new molecular entity (NME) which is manufactured, packaged and release tested by Gedeon Richter PLC, of Hungary. Based on solubility and the permeability studies, Cariprazine HCl is classified as a Class 2 drug (Low Solubility – High Permeability) as per the FDA Guidance for Biopharmaceutics Classification System. It is a white to off white (b)(4) powder with a molecular weight of 463.87 (b)(4). Cariprazine Hydrochloride drug substance has been fully characterized. The applicant references DMF 26321 for a complete description of the manufacturing process and all relevant characterization data pertaining to Cariprazine Hydrochloride. DMF 26321 has been reviewed and was determined to be adequate to support this application.

The drug product is being developed 1) for treatment of schizophrenia and 2) for the treatment of manic or mixed episodes associated with bipolar I disorder. The recommended dose range is (b)(4)

(b)(4) depending on the indication. The drug product is presented as 1.5, 3.0, 4.5, 6.0, (b)(4) mg immediate release capsules. The capsules are differentiated by markings and color: 1.5 mg potency is a size 4 (b)(4) capsule with a (b)(4) “FL 1.5” imprint on the body; 3 mg potency is a size 4 (b)(4) body and green to (b)(4) cap with a (b)(4) “FL 3” imprint on the body; 4.5 mg potency is a size 4 green to (b)(4) capsule with a (b)(4) “FL 4.5” imprint on the body; 6 mg potency is a size #3 capsule with a (b)(4) body and a (b)(4) cap with a (b)(4) “FL 6” imprint on the bod (b)(4)

(b)(4) The drug product formulation of the drug product includes the active, USP pregelatinized starch and USP, (b)(4) magnesium stearate.

Executive Summary Section

The common drug product specifications across all strengths include description, identification by HPLC and UV, content uniformity, assay, (b) (4), related substances, dissolution and microbiology. The description specification varies based on the capsule color and the dissolution specification for the 1.5, 3.0, 4.5 and 6.0 mg capsules (b) (4).

All potencies of the drug product are manufactured by Forest Laboratories Ireland, Ltd., Clonshaugh, Dublin, Ireland site with a typical batch size of (b) (4) kg. The batch formulas for the (b) (4) different strengths of the drug product are qualitatively identical. Each capsule contains the drug substance, pregelatinized starch and (b) (4) magnesium stearate. In all cases the batch size remains unchanged. To achieve the desired potency, (b) (4)

The applicant proposes three packaging presentations, blister packs, and 30-count, 60 cc HDPE bottles and 90 count 120 cc HDPE bottles. The sponsor proposes a storage condition of 25°C with excursions permitted in the range of 15°C – 30°C. The applicant has requested a 24 month expiry for all (b) (4) strengths of the drug product. The applicant included 24 months of long term and 6 months of accelerated primary stability data for 9 registration batches of the drug using a bracketed stability protocol. The batches were manufactured at a commercial scale and packaged in the intended commercial container closure systems. The bracketed protocol included 3 batches each of the highest and lowest strengths and one batch of each of the intermediate strengths. The samples were tested for description, assay, (b) (4) dissolution, related substances and microbial limits. All data were within the proposed specification limits and there were no unexpected stability trends observed. Accordingly, real-time stability data demonstrates that the drug product can be adequately stored in all container closure systems at 25° C/60%RH for 24 months when protected from light and supports the requested expiry. As such, we concur with the proposed 24-month expiration for the 1.5, 3.0, 4.5, 6.0, (b) (4) mg drug products packaged in both blisters and HDPE bottles.

Additionally, this application includes a comparability protocol which includes an alternate manufacturing site for the drug substance. The applicant outlined all of the manufacturing changes as well as the stability data to be included in the submission. The applicant proposes to submit these changes to the agency in the form of a CBE-30 supplement. The post marketing group and the Office of Compliance were consulted and both agreed with the filing category for the changes outlined in the comparability protocol. As such, the comparability protocol is acceptable.

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

Cariprazine Hydrochloride is being developed 1) for treatment of schizophrenia and 2) for the treatment of manic or mixed episodes associated with bipolar I disorder. The usual recommended dose range is (b) (4)

Executive Summary Section

(b) (4). Dosing may be with or without food. (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, this application is recommended for approval. The drug substance was determined to be safe, effective, and manufactured in a consistent manner with inherent quality in DMF 26321. The sponsor identified CQA and established controls to ensure the quality of the drug product. The results of the batch analyses confirm quality of the drug product at release. The intended commercial packaging presentations provide adequate protection of the drug product and ensure drug product quality over the proposed 24-month shelf-life as demonstrated through the drug product stability data. Additionally, the draft bottle labels and package insert are acceptable from a CMC perspective. The final recommendation from the Office of Compliance of acceptable was issued on October 7, 2013 (see appended EER Summary Report). The Division of Pharmaceutical Analysis (DPA) conducted methods validation and it has been concluded that the methods are acceptable for quality control and regulatory purposes.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date

OStephens

C. CC Block

Orig. NDA 204370

Chemistry Assessment Section

Method Validation for NDA 204370:

The Division of Pharmaceutical Analysis (DPA) evaluated the following methods:

- Assay Determination of Cariprazine HCl by HPLC (Analytical Procedure PRD-TM-ANL-00352)
- Determination of Cariprazine HCl Impurities by HPLC (Analytical Procedure PRD-TM-ANL-00353)
- Determination of (b) (4) by HPLC (Analytical Procedure PRD-TM-ANL-00173)
- Determination of (b) (4) and Degradation Products by HPLC (Analytical Procedure PRD-TM-ANL-00174)
- Identification, Assay and Content Uniformity by HPLC (Analytical Procedure PRD-TM-ANL-00132)

Upon completion of the evaluation of the aforementioned methods, the applicant was asked to make the following modifications or to provide justification for their proposed limits (see agency IR letter dated 10/17/ 2013).

1. Determination of (b) (4) by HPLC (Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00173)

- On page 6 of 15, under Working Standard Solution (Wstd) in Section H: System Suitability, the %RSD of the Peak Area Responses for the first six standard injections (Wstd) should be $\leq \frac{(b)}{(4)}\%$ (n=6) instead of $\leq \frac{(b)}{(4)}\%$ (n=6).
- On page 6 of 15, under Working Weight Check Solution (Wsq) in Section H: System Suitability, the limit for each weight check standard injection should be (b) (4)% instead of (b) (4) $\pm 5\%$.
- On page 9 of 15, Section J: Sample Analysis, the limit for each bracketing working standard injection should be (b) (4)% instead of (b) (4)%.

2. Determination of (b) (4) and Degradation Products by HPLC (Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00174)

- On page 5 of 15, under Working Standard Solution (Wstd) in Section G: System Suitability, the %RSD of the Peak Area responses for the first six standard injections (Wstd) should be $\leq \frac{(b)}{(4)}\%$ (n=6) instead of $\leq \frac{(b)}{(4)}\%$ (n=6)
- On page 5 of 15, under Working Weight Check Solution (Wsq) in Section G: System Suitability, the limit for each weight check standard injection should be (b) (4)% instead of (b) (4)%.
- On page 8 of 15, Section I: Sample Analysis, the limit for each bracketing working standard injection should be (b) (4)% instead of (b) (4)%.

The applicant responded on October 25, 2013 and agreed to implement the requested modifications to methods PRD-TM-ANL-00173 and PRD-TM-ANL-00174.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Establish Evaluation Report:

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 204370/000	Sponsor:	FOREST LABS INC
Org. Code:	130		HARBORSIDE FINANCIAL CENTER PLAZA 5
Priority:	1		JERSEY CITY, NJ 07311
Stamp Date:	19-NOV-2012	Brand Name:	CARIPRAZINE
PDUFA Date:	19-NOV-2013	Estab. Name:	
Action Goal:		Generic Name:	CARIPRAZINE
District Goal:	19-JUN-2013	Product Number; Dosage Form; Ingredient; Strengths	

002; CAPSULE; CARIPRAZINE; 3MG
 001; CAPSULE; CARIPRAZINE; 1.5MG
 003; CAPSULE; CARIPRAZINE; 4.5MG
 (b) (4)
 004; CAPSULE; CARIPRAZINE; 6MG

FDA Contacts:	S. MCLAMORE	Prod Qual Reviewer	3017961710
	T. BOUIE	Product Quality PM	3017961649
	K. UPDEGRAFF	Regulatory Project Mgr	3017962201
	C. TELE	Team Leader	3017961762

Overall Recommendation:	ACCEPTABLE	on 05-OCT-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 03-OCT-2013	by EES_PROD		
	ACCEPTABLE	on 03-OCT-2013	by J. WILLIAMS	()	3017964196
	ACCEPTABLE	on 23-AUG-2013	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 23-AUG-2013	by EES_PROD		
	PENDING	on 23-AUG-2013	by EES_PROD		
	PENDING	on 03-DEC-2012	by EES_PROD		
	PENDING	on 03-DEC-2012	by EES_PROD		

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

DMF No: AADA:
 Responsibilities: FINISHED DOSAGE PACKAGER
 Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 03-DEC-2012
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: 9611779 FEI: 3002806762
 CHEMICAL WORKS OF GIDEON RICHTER
 ESZTERGOMI UT 27
DMF No: DOROG, PF. 26, HUNGARY
 26321 **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-AUG-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-DEC-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-AUG-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: 2436921 FEI: 1000521508
FOREST LABORATORIES INC
FARMINGDALE, , UNITED STATES 117353900

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9616660 FEI: 3002806993
FOREST LABORATORIES IRELAND, LTD.
CLONSHAUGH BUSINESS AND TECHNOLOGY PARK
DUBLIN 17, CLONSHAUGH, IRELAND

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 1523957 FEI: 1523957
FOREST PHARMACEUTICALS INC
CINCINNATI, , UNITED STATES 45209

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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/s/

SHERITA D MCLAMORE
10/30/2013

OLEN M STEPHENS
10/30/2013

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

METHODS VALIDATION REPORT SUMMARY

TO: Sherita McLamore-Hines, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Sherita.McLamore-Hines@fda.hhs.gov
Phone: (301)-796-1710
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehay, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: John Kauffman, Acting Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 204370

Name of Product: Cariprazine Capsules, 1.5 mg, 3 mg, 4.5 mg, 6 mg, (b) (4)

Applicant: Forest Laboratories Inc.

Applicant's Contact Person: Melina Cioffi

Address: Harborside Financial Center, Jersey City, NJ 07311

Telephone: (b) (6) Fax: (631) 858-7921

Date Methods Validation Consult Request Form Received by DPA: 11/27/12

Date Methods Validation Package Received by DPA: 11/27/12

Date Samples Received by DPA: 12/14/12

Date Analytical Completed by DPA: 8/9/13

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: Analyst's comments and suggested changes are in attached report. The analyst suggests that the system suitability requirements for methods PRD-TM-ANL-00173 and PRD-TM-ANL-00174 could be tightened as shown in attached memo based on results at DPA.

Analyst's work sheets and chromatograms are available at

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8804c7218>



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

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

Date: October 15, 2013
To: Sherita McLamore-Hines, CMC Reviewer
Through: John Kauffman, Deputy Director, Division of Pharmaceutical Analysis
From: Wei Ye, Chemist
Subject: Method Validation for NDA 204370
Cariprazine Capsules, 1.5 mg, 3 mg, 4.5 mg, 6 mg, (b) (4)
Forest Laboratories Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Identification, Assay and Content Uniformity by HPLC
(Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00132)
2. Assay Determination of Cariprazine HCl by HPLC
(Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00352)
3. Determination of Cariprazine HCl Impurities by HPLC
(Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00353)

The following methods were evaluated and are acceptable for quality control and regulatory purposes with the following suggested modifications:

4. Determination of (b) (4) by HPLC
(Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00173)
 - On page 6 of 15, under Working Standard Solution (Wstd) in Section H: System Suitability, the %RSD of the Peak Area Responses for the first six standard injections (Wstd) should be $\leq \frac{(b)}{(4)}\%$ (n=6) instead of $\leq \frac{(b)}{(4)}\%$ (n=6).
 - On page 6 of 15, under Working Weight Check Solution (Wsq) in Section H: System Suitability, the limit for each weight check standard injection should be $\frac{(b)}{(4)}\%$ instead of $\frac{(b)}{(4)}\%$.
 - On page 9 of 15, Section J: Sample Analysis, the limit for each bracketing working standard injection should be $\frac{(b)}{(4)}\%$ instead of $\frac{(b)}{(4)}\%$.
5. Determination of (b) (4) and Degradation Products by HPLC
(Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00174)
 - On page 5 of 15, under Working Standard Solution (Wstd) in Section G: System Suitability, the %RSD of the Peak Area responses for the first six standard injections (Wstd) should be $\leq \frac{(b)}{(4)}\%$ (n=6) instead of $\leq \frac{(b)}{(4)}\%$ (n=6).
 - On page 5 of 15, under Working Weight Check Solution (Wsq) in Section G: System Suitability, the limit for each weight check standard injection should be $\frac{(b)}{(4)}\%$ instead of $\frac{(b)}{(4)}\%$.
 - On page 8 of 15, Section I: Sample Analysis, the limit for each bracketing working standard injection should be $\frac{(b)}{(4)}\%$ instead of $\frac{(b)}{(4)}\%$.

Analyst's work sheets and chromatograms are available at
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8804c7218>

Summary of Results (Cont'd)

NDA 204370

Identification, Assay and Content Uniformity by HPLC
(Forest Laboratories Inc., Analytical Procedure PRD-TM-ANL-00132)

Results:

Assay

Dosage	Sample	mg/capsule	%LC	Avg. (2) (b) (4)

Limit:

90.0% - 110.0% of label claim

Content Uniformity

Dosage	Sample	mg/capsule	%LC	Avg. (3)	SD	AV (b) (4)

Limit:

AV < (b) (4)

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/s/

MICHAEL L TREHY
10/16/2013

JOHN F KAUFFMAN
10/17/2013

Vraylar (cariprazine) Capsules

NDA 204-370

Summary Basis for Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Forest Laboratories, Inc.,
Haborside Financial Center, Plaza V, suite 1900
Jersey City, NJ 07311

Indication: For the treatment of schizophrenia and the treatment of manic episodes associated with bipolar 1 disorder.

Presentation: The product will be available in ^(b)₍₄₎ different strengths; 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, ^(b)₍₄₎. The different strength capsules are differentiated by color, markings. The capsules will be packaged in HDPE bottles and blisters.

EER Status: Overall recommendation is “Acceptable” as of 5-Oct-2013.

Consults: ONDQA Biopharmaceutics – Acceptable as per Dr. Sandra Suarez-Sharp review dated 07-16-2013.

Methods Validation – Acceptable by FDA labs (14-Aug-2013). The reviewer will follow up with FDA labs comments to the applicant. This does not have any impact on the CMC recommendation.

EA – Categorical exclusion granted.

Post-Approval Agreements: None

Drug Substance:

The drug substance, cariprazine hydrochloride, is a new molecular entity. The drug substance is a white to off-white (b) (4) solid with molecular weight of 463.87. The drug substance is non-hygroscopic. (b) (4)

The drug substance synthesis and controls have been described in a DMF and the DMF was found to be adequate to support this application by the reviewer

Additionally, the drug substance quality is ensured through in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, assay, impurities, particle size distribution, residual solvents, heavy metals, and (b) (4). The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4) months.

Drug product:

Vraylar (cariprazine) capsules are an immediate release product to be marketed in (b) (4) different strengths. The drug product formulation uses standard compendial excipients with all capsules having the same fill weight. (b) (4)

The manufacturing process includes (b) (4)

The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for description, identification, assay, content uniformity, (b) (4), dissolution, microbial purity and degradation products. The analytical procedures for the drug product are adequately described and validated. The provided stability data support a 24-month expiration period for this product.

The drug product is stored at 25°C with excursions permitted 15-30°C (59-86°F).

Additionally, the applicant has proposed a comparability protocol to qualify an alternate site for the drug substance manufacturing. The protocol was reviewed and found to be acceptable by the primary reviewer.

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The application is recommended for “**Approval**” from CMC perspective.

Ramesh K. Sood, Ph.D.
Acting Director, DPA I/ONDQA

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/s/

RAMESH K SOOD
10/10/2013

NDA 204-370

Cariprazine HCl Capsules

1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg

(b) (4)

Forest Laboratories, Inc

Sherita D. McLamore-Hines, Ph.D.

Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA: 204-370
2. REVIEW: #1
3. REVIEW DATE: July 18, 2013
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

n/a

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

November 19, 2012

Amendment

December 13, 2012

Amendment

April 8, 2013

Amendment

February 26, 2013

Amendment

February 8, 2013

Amendment

June 14, 2013

Amendment

July 9, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:

Forest Laboratories, Inc

Address:

Harborside Financial Center

Plaza V, Suite 1900

Jersey City, NJ 07311

Chemistry Review Data Sheet

Representative: n/a

Telephone: 201.427.8326

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name (USAN): Cariprazine HCl
- c) Code Name/# (ONDC only): RGH-188
- d) Chem. Type/Submission
 - Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Schizophrenia and Treatment of Manic Episodes Associated with Bipolar I Disorder

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg (b) (4)

13. ROUTE OF ADMINISTRATION: oral

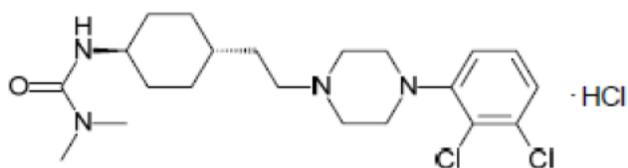
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

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

Chemical Name: *trans*-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl-N',N'-dimethylurea hydrochlorideMolecular Formula: C₂₁H₃₂Cl₂N₄O · HCl

Molecular Weight: 463.87

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
26321	II	Geodeon Richter Plc	Drug Substance	1	Adequate	6/28/2013	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A
	III			4	n/a		N/A

¹ 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")

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	26321	Synthesis of the drug substance

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	Acceptable	07/16.2013	Sandra Suarez
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Categorical Exclusion 21 CFR 25 31(b) <i>Acceptable</i>	07/11/2013	Sherita McLamore, Ph.D.
Microbiology	N/A	N/A	

Executive Summary Section

The Chemistry Review for NDA 204-370**The Executive Summary****A. Recommendation and Conclusion on Approvability**

At this time a recommendation for the Chemistry, Manufacturing, and Controls (CMC) section of NDA 204-370 is pending. The approval from a CMC standpoint is contingent on an acceptable recommendation from the Office of Compliance.

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

There are no CMC Phase 4 activity recommendations.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Cariprazine Hydrochloride has been identified as the active pharmaceutical ingredient in this application. Cariprazine Hydrochloride is a new molecular entity (NME) which is manufactured, packaged and release tested by Gedeon Richter PLC, of Hungary. Based on solubility and the permeability studies, Cariprazine HCl is classified as a Class 2 drug (Low Solubility – High Permeability) as per the FDA Guidance for Biopharmaceutics Classification System. It is as a white to off white (b) (4) powder with a molecular weight of 463.87 and has no reported melting point (degrades before melting). Cariprazine Hydrochloride drug substance has been fully characterized. The applicant references DMF 26321 for a complete description of the manufacturing process and all relevant characterization data pertaining to Cariprazine Hydrochloride. DMF 26321 has been reviewed and was determined to be adequate to support this application.

The drug product is being developed for the treatment of schizophrenia and manic and mixed episode associated with Bipolar I Disorder. The recommended dose range is (b) (4)

(b) (4) depending on the indication. The drug product is presented as 1.5, 3.0, 4.5, 6.0, (b) (4) mg immediate release capsules. The capsules are differentiated by markings and color: 1.5 mg potency is a size 4 (b) (4) capsule with a (b) (4) “FL 1.5” imprint on the body; 3 mg potency is a size 4 (b) (4) body and (b) (4) cap with a (b) (4) “FL 3” imprint on the body; 4.5 mg potency is a size 4 (b) (4) capsule with a (b) (4) “FL 4.5” imprint on the body; 6 mg potency is a size #3 capsule with a (b) (4) body and a (b) (4) cap with a (b) (4) “FL 6” imprint on the body; (b) (4)

The drug

Executive Summary Section

product formulation of the drug product includes the active, USP pregelatinized starch and USP, (b) (4) magnesium stearate.

The common drug product specifications across all strengths include description, identification by HPLC and UV, content uniformity, assay, (b) (4), related substances, dissolution and microbiology. The description specification varies based on the capsule color and the dissolution specification for the 1.5, 3.0, 4.5 and 6.0 mg capsules (b) (4).

All potencies of the drug products are manufactured by Forest Laboratories Ireland, Ltd., Clonsbaugh, Dublin, Ireland site with a typical batch size of (b) (4) kg. The batch formulas for the (b) (4) different strengths of the drug product are qualitatively identical. Each capsule contains the drug substance, pregelatinized starch and (b) (4) magnesium stearate. In all cases the batch size remains unchanged. To achieve the desired potency, (b) (4)

The applicant proposes three packaging presentations, blister packs, and 30-count, 60 cc HDPE bottles and 90 count 120 cc HDPE bottles. The sponsor proposes a storage condition of 25°C with excursions permitted in the range of 15°C – 30°C. The applicant has requested a 24 month expiry for all (b) (4) strengths of the drug product. The applicant included 24 months of long term and 6 months of accelerated primary stability data for 9 registration batches of the drug using a bracketed stability protocol. The batches were manufactured at a commercial scale and packaged in the intended commercial container closure systems. The bracketed protocol included 3 batches each of the highest and lowest strengths and one batch of each of the intermediate strengths. The samples were tested for description, assay, (b) (4) dissolution, related substances and microbial limits. All data were within the proposed specification limits and there were no unexpected stability trends observed. Accordingly, real-time stability data demonstrates that the drug product can be adequately stored in all container closure systems at 25° C/60%RH for 24 months when protected from light and supports the requested expiry. As such, we concur with the proposed 24-month expiration for the 1.5, 3.0, 4.5, 6.0, (b) (4) mg drug products packaged in both blisters and HDPE bottles.

Additionally, this application includes a comparability protocol which includes an alternate manufacturing site for the drug substance. The applicant outlined all of the manufacturing changes as well as the stability data to be included in the submission. The applicant proposes to submit these changes to the agency in the form of a CBE-30 supplement. The post marketing group and the Office of Compliance were consulted and both agreed with the filing category for the changes outlined in the comparability protocol. As such, the comparability protocol is acceptable.

Executive Summary Section

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

Cariprazine Hydrochloride is being developed for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. The usual recommended dose range is [REDACTED] (b) (4)

[REDACTED] Dosing may be with or without food. [REDACTED] (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

A recommendation for the approvability of NDA 204370 from a CMC perspective can not be determined until final recommendations are received from the Office of Compliance regarding the site inspections.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

SMcLamore/Date

RSood

C. CC Block

Orig. NDA 204370

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

S DRUG SUBSTANCE [Cariprazine Hydrochloride, Forest Laboratories.]
Cariprazine Hydrochloride is the active pharmaceutical ingredient in this application. The applicant included very little relevant information pertaining to the manufacture and control of the drug substance but referenced DMF 26321 for detailed information pertaining to the manufacture and control of this drug substance in the application. DMF 26321 was reviewed in conjunction with this submission and was deemed adequate to support the intended use.

S.1 General Information

S.1.1 Nomenclature

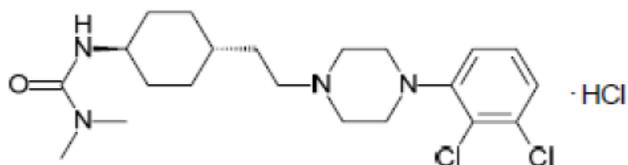
IUPAC: *trans*-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl-N',N'-dimethylurea hydrochloride

USAN: Cariprazine HCl

Code Name: RGH-188 HCl

CAS Registry Number: 1083076-69-0

S.1.2 Structures



S 1.3 General Properties

This drug substance is a non-hygroscopic, white to off-white (b) (4) powder with a molecular formula $C_{21}H_{32}Cl_2N_4O \cdot HCl$ of and a molecular mass of 463.87. The drug substance has a BCS classification as Class 2 (low solubility, high permeability) according to the FDA Guidance¹ for Biopharmaceutics Classification System (BCS). The drug substance has (b) (4) and a particle size distribution of D_{10} NMT (b) (4) μm ; D_{50} NMT (b) (4) μm and D_{90} NMT (b) (4) μm . The applicant indicates that the drug substance exist in (b) (4). The drug substance solubility profile is included below in table 1.

Chemistry Assessment Section

Table 1: Cariprazine Hydrochloride Drug Substance Solubility Profile

Isopropanol	Practically insoluble
N,N-DMF	Practically insoluble
Acetone	Very Slightly Insoluble
Acetonitrile	Very Slightly Insoluble
(b) (4)	Very Slightly Insoluble
Dichloromethane	Slightly Insoluble
Ethanol	Slightly Insoluble
Methanol	Freely Soluble

In the pH range of 1 to 5.5, the drug substance exhibits BCS Class 1 characteristics (High Solubility-High Permeability). The pH solubility of the drug substance is included in Table 2 below.

Table 2: Drug Substance Solubility

<i>pH</i>	<i>Solubility (mg/mL)</i>
1	3.2579
2	8.9336
3	11.0321
4	3.2303
5	0.3510
5.5	0.1488
6	0.0188
7	0.0013

Evaluation: Adequate

The applicant has provided adequate general information (i.e. names, structure, molecular formula, molecular weight, physicochemical properties) about the drug substance. The information provided pertaining to the general description of the drug substance is sufficient to support this application. Additional information can be found in DMF 26321 for which the applicant had provided the appropriate letter of authorization.

S.2 Manufacture**S.2.1 Manufacturers**

Manufacturing, packaging, release and stability testing of the drug substance will be performed by:

Gedeon Richter Plc.

Dorog, Esztergomi út 27

Hungary, H-2510

The commercial drug substance will be manufactured, packaged and release tested by Gedeon Richter Plc of Hungary. (CFN 9610753). The Gedeon site was entered into the EES system in December of 2012 and is currently awaiting inspection (planned completion May 24, 2013).

Chemistry Assessment Section

S.2.2 Description of Manufacturing Process and Process Controls

The applicant provides a brief description of the manufacturing process and references DMF 26321 for all aspects pertaining to the manufacture and control of the drug substance. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

(b) (4)



Chemistry Assessment Section

S.2.3 Control of Materials

The applicant references DMF 26321 for all aspects pertaining to the control of the materials. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

S.2.4 Controls of Critical Steps and Intermediates

The applicant references DMF 26321 for all aspects pertaining to the control of critical steps and intermediates. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

S.2.5 Process Validation and/or Evaluation

The applicant references DMF 26321 for all aspects pertaining to the manufacture and control of the drug substance. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

S.2.6 Manufacturing Process Development

The applicant references DMF 26321 for all aspects pertaining to the manufacturing process development. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

S.3 Characterization**S.3.1 Elucidation of Structure and other Characteristics**

The applicant references DMF 26321 for all aspects pertaining to the structure elucidation and characterization. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

S.3.2 Impurities

The applicant listed the five specified impurities in the drug substance and included their content in the 9 registration batches. The levels ranged from less than (b) (4) % to (b) (4) % with the total impurities not exceeding (b) (4) %. These impurities are included in the drug substance specification and are listed below in Table 3. A complete description and discussion (including characterization data and the analytical method used for the determination) of all of the impurities related to the drug substance is included in DMF 26321.

Table 3

Chemistry Assessment Section

<i>Name</i>	<i>Chemical Name</i>	<i>Structure</i>	<i>Origin</i>	<i>Maximum Level Observed (%)</i>
(b) (4)				

Chemistry Assessment Section

Table 4: Specified Impurities Content in Drug Substance Batches

<i>Potential Impurity</i>	<i>Batch Number</i>								
	<i>L77111K</i>	<i>L78004K</i>	<i>L8A143A</i>	<i>L8B030F</i>	<i>L8B057F</i>	<i>L06038N</i>	<i>L06042D</i>	<i>L19068N</i>	<i>L27051N</i>
	<i>(%)</i>								
(b) (4)									

S.4 Control of Drug Substance

S.4.1 *Specification*

The applicant indicates that the drug substance is tested from the manufacturer as indicated in DMF 26321. The drug substance specifications are included below in Table 5 which has been reproduced from the application.

Chemistry Assessment Section

Table 5: Drug Substance Specification

<i>Test</i>	<i>Acceptance Criteria</i>		<i>Analytical Procedure</i>
Description ^a	White to almost white	(b) (4) powder	Visual
Identifications			
A	(b) (4)	(b) (4)	(b) (4)
B (HPLC)	Retention time compares to standard		PRD-TM-ANL-00352
C	(b) (4)	(b) (4)	USP < 191 >
(b) (4)	NMT	(b) (4) %	(b) (4)
Assay ^a	(b) (4) %	(b) (4)	PRD-TM-ANL-00352
Residue on Ignition	NMT	(b) (4) %	USP < 281 >
Heavy Metals	NMT	(b) (4) ppm	USP < 231 > Method II
Metal Residue (b) (4)	NMT	(b) (4) ppm	PRD-TM-ANL-00128
Residual Solvents			
(b) (4)	NMT	(b) (4) ppm	PRD-TM-ANL-00675
(b) (4)	NMT	(b) (4) ppm	
(b) (4)	NMT	(b) (4) ppm	
(b) (4)	NMT	(b) (4) ppm	
(b) (4)	NMT	(b) (4) ppm	
(b) (4)	NMT	(b) (4) ppm	
Impurities ^a			
(b) (4)	≤	(b) (4) %	PRD-TM-ANL-00353
(b) (4)	≤	(b) (4) %	
(b) (4)	≤	(b) (4) %	
(b) (4)	≤	(b) (4) %	
(b) (4)	≤	(b) (4) %	
(b) (4)	≤	(b) (4) %	
Unspecified (each)	≤	(b) (4) %	PRD-TM-ANL-00968
Total (specified and unspecified)	≤	(b) (4) %	
(b) (4)	NMT	(b) (4) ppm	
Particle Size	D ₁₀	NMT (b) (4) μm	PRD-TM-ANL-00354
	D ₅₀	NMT (b) (4) μm	
	D ₉₀	NMT (b) (4) μm	
Microbiology ^a	Total aerobic microbial count	NMT (b) (4) cfu/g	USP < 61 > and < 62 >
	Total combined molds and yeasts count	NMT (b) (4) cfu/g	
	<i>Escherichia coli</i>	Absence in (b) (4) g	

a Tests performed at retest and stability

The applicant included the regulatory specifications for the drug substance. The acceptance criteria for the related compound (b) (4) which is a potentially genotoxic material is above the accepted limit ((b) (4) μg/day). This issue was conveyed to the DMF holder and was addressed within the review of DMF 26321. The agency and holder worked together and the

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acceptance criterion was adjusted to NMT (b) (4)%. While at the maximum daily dose of (b) (4), it is consistent with the holder's manufacturing capabilities and was deemed acceptable by the Pharm/Tox reviewer Dr. Elzbieta Chalecka-Franaszek.

Comment 1 from Agency's June 5, 2013 Information Request Letter:

Provide the full specification that you will use to release drug substance batches.

Summary of Holder's June 14, 2013 Response: The applicant indicates that upon receipt the drug product manufacturer will fully test all batches of the drug substance according to the regulatory specification.

Evaluation: Adequate

S.4.2 Analytical Procedures

The applicant includes the following analytical procedures to release the drug substance: Particle Size, Assay for (b) (4), Assay of Cariprazine, impurities, residual solvents and determination of (b) (4) content.

Evaluation: Adequate – The proposed methods are appropriate and capable of testing for and controlling the assay, identification, particle size and related substance in the drug substance.

S.4.3 Validation of Analytical Procedures

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The applicant provided validation information pertaining to the assay, identification and related substances. The information has been summarized in the tables below.

The applicant includes a complete description of the assay, identification and related substances analytical procedures. The description of the procedures includes the principle, reagents, equipment, evaluation, assessment and sample spectra where applicable. Summaries of each of the validation reports are included in the tables below.

Table 6: Assay and Identification by HPLC

<i>Parameter</i>	<i>Results</i>
Specificity	<ul style="list-style-type: none">no detectable solvent peaks observed at the retention time of the active substance in the chromatogramassures selective separation between cariprazine and all known impurities and degradation products ($R_s > 1.5$)
	Under normal conditions: <ul style="list-style-type: none">$R_s > 1.5$ for cariprazine and impurities eluted immediately before and after Stress test: <ul style="list-style-type: none">degradation products have no influence on the assay determination

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Solution Stability	<ul style="list-style-type: none"> RSD < 1.0% reference solution is stable for 23 hours system suitability solution is stable for 51.5 hours no tendency observed between data
Linearity	<ul style="list-style-type: none"> $r^2 > 0.999$ confidence interval of Y intercept includes the origin (P = 95%) residuals are distributed uniformly without tendency around the regression line linearity range from 0.16 µg/ml to 0.24 µg/ml (80% to 120%)
Accuracy	<ul style="list-style-type: none"> t-test of the measurements results, $t_{\text{calc}} < t_{\text{crit}}$ (P = 95%)
Precision	<p>Repeatability:</p> <ul style="list-style-type: none"> RSD < 1.0% <p>Intermediate Precision:</p> <ul style="list-style-type: none"> RSD < 1.0% $F_{\text{calc}} < F_{\text{crit}}$ (P = 95%), there are no significant differences between the variances between and within groups
Robustness and ruggedness tests	<ul style="list-style-type: none"> Change in wavelength, temperature of the column space, ratio of the organic-aqueous phase of mobile phase B, concentration of the (b) (4) buffer, and results obtained with different column and with different apparatus, practically has no influence on measurement results (within the limits applied)

Table 7: Metal Residue (b) (4) by ICP

Chemistry Assessment Section

<i>Parameter</i>	<i>Results</i>
Specificity	<ul style="list-style-type: none"> profiles of the individual samples do not differ from each other no new peaks or distortions were observed in the test window $e = \frac{(b)}{(4)}$
Linearity	<ul style="list-style-type: none"> $r^2 = \frac{(b)}{(4)}$ confidence interval of Y intercept includes the origin ($P = \frac{(b)}{(4)}\%$) residuals are distributed uniformly without tendency around the regression line linearity range from $\frac{(b)}{(4)}$
Accuracy	<ul style="list-style-type: none"> mean recovery = $\frac{(b)}{(4)}$ individual recoveries: $\frac{(b)}{(4)}$
Precision	Repeatability: <ul style="list-style-type: none"> RSD = $\frac{(b)}{(4)}\%$ ($n = 7, \leq \frac{(b)}{(4)}\%$) Intermediate Precision: <ul style="list-style-type: none"> RSD = $\frac{(b)}{(4)}\%$ ($n = 9, \leq \frac{(b)}{(4)}\%$) $\Delta = \frac{(b)}{(4)}\%$ ($\leq \frac{(b)}{(4)}\%$) $\frac{(b)}{(4)}$ ($F_{calc} < F_{crit}$) there are no significant differences between the variances between and within groups ($P = \frac{(b)}{(4)}\%$)
Detection Limit	<ul style="list-style-type: none"> DL = $\frac{(b)}{(4)}$ $\mu\text{g/g}$
Quantitation Limit	<ul style="list-style-type: none"> QL = $\frac{(b)}{(4)}$ $\mu\text{g/g}$ RSD_{QL} < $\frac{(b)}{(4)}\%$ ($n = 5$)

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Table 8: Determination of Residual Solvent by GC

<i>Parameter</i>	<i>Results</i>
Specificity	<ul style="list-style-type: none"> traces of impurities presented in the diluent do not influence determination of residual solvents of cariprazine HCl drug substance no significant interferences observed at retention times of residual solvent peaks selective separation between all residual solvents ($R_s > \frac{(b)}{(4)}$)
Linearity	<ul style="list-style-type: none"> $r^2 > \frac{(b)}{(4)}$ confidence interval of Y intercept includes the origin ($P = \frac{(b)}{(4)}\%$) residuals are distributed uniformly without tendency around the regression line
	(b) (4) linearity range: (b) (4) $\mu\text{g/ml}$
	(b) (4) linearity range: (b) (4) $\mu\text{g/ml}$
	(b) (4) linearity range: (b) (4) $\mu\text{g/ml}$
	(b) (4) linearity range: (b) (4) $\mu\text{g/ml}$
	(b) (4) linearity range: (b) (4) $\mu\text{g/ml}$
Accuracy	<ul style="list-style-type: none"> $r^2 > \frac{(b)}{(4)}$ confidence interval of Y intercept includes the origin ($P = \frac{(b)}{(4)}\%$) residuals are distributed uniformly without tendency around the regression line individual recoveries: $\frac{(b)}{(4)}\%$
	(b) (4) mean recovery = (b) (4) %
	(b) (4) mean recovery = (b) (4) %
	(b) (4) mean recovery = (b) (4) %
	(b) (4) mean recovery = (b) (4) %
	(b) (4) mean recovery = (b) (4) %
Precision	Repeatability: <ul style="list-style-type: none"> $RSD < \frac{(b)}{(4)} (n = 7)$ Intermediate Precision: <ul style="list-style-type: none"> $RSD < \frac{(b)}{(4)} (n = 21)$ $F_{\text{calc}} < F_{\text{crit}} (P = \frac{(b)}{(4)})$, there are no significant differences between the variances between and within groups
Detection Limit	For all residual solvents: <ul style="list-style-type: none"> $DL = \frac{(b)}{(4)} \text{ppm}$ signal/noise ratio $> \frac{(b)}{(4)}$ for all solvents
Quantitation Limit	For all residual solvents: <ul style="list-style-type: none"> $QL = \frac{(b)}{(4)} \text{ppm}$ signal/noise ratio $> \frac{(b)}{(4)}$ for all solvents $RSD_{QL} < \frac{(b)}{(4)}\%$

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Table 9: Related Substances by HPLC

Parameter	Results	
Specificity	<ul style="list-style-type: none"> no detectable solvent peaks observed at the retention time of the analyte in the chromatogram (b) (4) 	
Linearity	<ul style="list-style-type: none"> $r^2 > (b) (4)$ confidence interval of the Y intercept includes origin ($P = 95\%$) residuals distribute randomly, without tendency around regression line 	
	Cariprazine (RGH-188)	linearity range: 0.18 – 11.0 µg/ml (0.02 - 1.20%)
	(b) (4)	linearity range: (b) (4) µg/ml (b) (4)
	(b) (4)	linearity range: (b) (4) µg/ml
	(b) (4)	linearity range: (b) (4) µg/ml
	(b) (4)	linearity range: (b) (4) µg/ml
	(b) (4)	linearity range: (b) (4) µg/ml
Accuracy	<ul style="list-style-type: none"> $r^2 > (b) (4)$ confidence interval of the Y intercept includes origin ($P = (b) (4) \%$) confidence interval of slope includes 1 ($P = (b) (4) \%$) residuals are distributed uniformly without tendency around the regression line individual recoveries: (b) (4) % 	
	(b) (4)	mean recovery = (b) (4) %
	(b) (4)	mean recovery = (b) (4) %
	(b) (4)	mean recovery = (b) (4) %
	(b) (4)	mean recovery = (b) (4) %
	(b) (4)	mean recovery = (b) (4) %
Detection Limit	For all impurities: <ul style="list-style-type: none"> $DL = (b) (4) \%$ signal/noise ratio $> (b) (4)$ for all impurities 	
Quantitation Limit	For all impurities: <ul style="list-style-type: none"> $QL = (b) (4) \%$ $RSD_{QL} < (b) (4) \%$ 	
Precision	Repeatability:	
	<ul style="list-style-type: none"> $RSD < (b) (4)$, $n = 6$ 	
	Intermediate Precision:	
Robustness	<ul style="list-style-type: none"> $RSD < (b) (4)$, $n = 3$ $F_{calc} < F_{crit}$ ($P = (b) (4) \%$), there are no significant differences between the variances between and within groups 	
	<ul style="list-style-type: none"> Change in wavelength, temperature of the column compartment, flow rate, amount of the organic solvent content of the (b) (4) concentration of the (b) (4) practically has no influence on test results (within the used ranges) 	
Solution Stability	<ul style="list-style-type: none"> $RSD < (b) (4) \%$ system suitability, reference and test solutions are stable for (b) (4) hours 	

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Table 10: ^{(b) (4)} by UPLC

<i>Parameter</i>	<i>Results</i>
Specificity	^{(b) (4)}
Detection Limit	
Quantitation Limit	
Linearity	
Accuracy	
Precision	
Solution Stability	

Chemistry Assessment Section

Table 11: Particle Size Distribution

<i>Parameter</i>	<i>Results</i>
Precision	(b) (4)
Linearity	
Range	
Robustness	

Evaluation: *adequate*

The applicant provided the results of the analytical procedures validation activities. The applicant validated all methods for specificity, linearity, precision, robustness, range, and accuracy. The applicant established the LOD and LOQ limits for the drug related impurities HPLC method. The results confirm that the methods are capable of testing the drug product identity, purity, strength, and performance. The information provided is adequate to support the approval of this application.

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S.4.4 Batch Analyses

The references DMF 26321 for the tabulated summary of the drug substance batch analyses and does not include any additional information.

Evaluation: *adequate*

The applicant did not provided batch analyses for the drug substances in the original submission. The applicant was asked to provide representative batch analyses for the drug substances that were used to manufacture the primary stability batches. The applicant responded and provided the request information (see below).

Comment 2 from Agency's June 5, 2013 Information Request Letter

Provide batch analysis for the drug substance batches used to manufacture the primary stability batches. Summary of Holder's June 14, 2013 Response: The applicant provided batch analyses for the three registration stability batches of the drug substance (see table 12 below).

Table 12: Batch Analysis for Drug Substance Batches used in Registration Stability Batches

Test	Acceptance Criteria	Results		
		8002587-01 (L8B030F)	8002587-02 (L8A143A)	8002587-03 (L8B057F)
Description	White to almost white (b) (4) powder	Conforms	Conforms	Conforms
Identifications				
A (b) (4)	(b) (4)			
B (HPLC)	(b) (4)			
C	(b) (4)			
Assay				
Residue on Ignition				
Heavy Metals				
Metal Residue (b) (4)	(b) (4)			
Residual Solvents				
(b) (4)				

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Impurities		(b) (4)
Particle Size		D ₁₀
		D ₅₀
		D ₉₀
Microbiology	Total aerobic microbial count	align="right">(b) (4)
	Total combined molds and yeasts count	
	<i>Escherichia coli</i>	

Evaluation: Adequate

S.4.5 Justification of Specification

The applicant provided justification for the following acceptance criteria: identification, description, particle size distribution, (b) (4), metal residue, related substances and assay.

Description:

The drug substance is visually examined for appearance and compared to the proposed acceptance criteria for description as part of release and stability testing.

Particle Size Distribution

The current propose acceptance criteria for the PSD is d₁₀: NMT (b) (4) μm; d₅₀: NMT (b) (4) μm and d₉₀: NMT (b) (4) μm. The PSD specification was necessary to insure a homogenous distribution of the API in the drug product. The PSD specification was set based on batch history (see table 13 below).

Table 13: PSD Batch History Data

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Batch Number	Particle Size Distribution (μm)					
	d_{10}	d_{10} limit	d_{50}	d_{50} limit	d_{90}	d_{90} limit
L77111K	(b) (4)		(b) (4)		(b) (4)	
L78004K						
L8A143A						
L8B030F						
L8B057F		NMT (b) (4) μm		NMT (b) (4) μm		NMT (b) (4) μm
L06038N						
L06042D						
L19068N						
L27051N						

(b) (4)

Identification by HPLC:

The drug substance is released based on comparison of the retention time of the min peak. All batches have complied.

(b) (4)

Test is performed using USP methods and standards

(b) (4)

Metal Residue (b) (4)

The applicant indicates that an ICP method was developed and validated for the determination of (b) (4). The acceptance criterion for (b) (4) (NMT (b) (4) ppm) was established based on the batch release data and the recommendation in USP <231>. The results for all batches manufactured to date have complied with this specification.

Related Substances:

The acceptance criteria and batch history data are for the related substances are included in Table 14 below:

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The acceptance criteria for the residual solvents are all based data form the plant scale batches (see table below). The proposed limits are consistent with the manufacturing capability and in most cases tighter than the ICH guidelines for these most solvents.

Table 16: Residual Solvent Levels

Residual Solvent	Batch Number								
	L77111K	L78004K	L8A143A	L8B030F	L8B057F	L06038N	L06042D	L19068N	L27051N
	(ppm)								
(b) (4)									

Evaluation: *adequate*

All of the proposed tests and acceptance criteria are adequate based on batch release data and stability data. The proposed acceptance criteria are consistent with the holder's manufacturing capability and in some cases are tighter than those recommended in ICH Q6A. The proposed tests and acceptance criteria are adequate to ensure the quality of the API and are acceptable to support the approval of the pending NDA.

S.5 Reference Standards or Materials

The applicant references DMF 26321 for information pertaining to the reference standard. DMF 26321 was reviewed in conjunction with this submission and found adequate to support this application.

S.6 Container Closure System

The applicant indicates that the drug substance will be stored in (b) (4) but references DMF 26321 for all relevant details pertaining to the container closure system. DMF 26321 was reviewed in conjunction with this application and found adequate to support this application.

Chemistry Assessment Section

S.7 Stability**S.7.1 Stability Summary and Conclusions**

The applicant indicates that (b) (4) stability data is currently available for the drug substance. The applicant further indicates that this data supports a (b) (4) year re-test date and reference DMF 26321 for specific details pertaining to the stability data. DMF 26321 was reviewed in conjunction with this application and found adequate to support this application

P DRUG PRODUCT

P.1 The drug product, Cariprazine Hydrochloride Capsules, is a new molecular entity that is being developed for the treatment of schizophrenia and manic and mixed episode associated with Bipolar I Disorder. The recommended dose range is (b) (4) depending on the indication. The drug product is presented as 1.5, 3.0, 4.5, 6.0, (b) (4) mg immediate release capsules. The capsules are differentiated by markings and color: 1.5 mg potency is a size 4 (b) (4) capsule with a (b) (4) “FL 1.5” imprint on the body; 3 mg potency is a size 4 (b) (4) body and (b) (4) cap with a (b) (4) “FL 3” imprint on the body; 4.5 mg potency is a size 4 (b) (4) capsule with a (b) (4) “FL 4.5” imprint on the body; 6 mg potency is a size #3 capsule with a (b) (4) body and a (b) (4) cap with a (b) (4) “FL 6” imprint on the body;

(b) (4) The drug product formulation of the drug product includes the active, USP pregelatinized starch and USP, (b) (4) magnesium stearate. The typical batch size for the drug product is (b) (4) kg. The batch formulas are all qualitatively identical. In each case, (b) (4)

P.2 Pharmaceutical Development**P.2.1 Components of the Drug Product**

The drug product compositions are included in the table below which has been reproduced from the application.

Table 17: Drug Product Composition**1.5 mg Drug Product**

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<i>Component</i>	<i>Pharmaceutical Function</i>	<i>Quality Standard</i>	<i>Unit Dose Composition</i>	
			<i>(% w/w)</i>	<i>(mg/capsule)</i>
Cariprazine HCl	Drug Substance	In-house ^a		(b) (4)
Pregelatinized starch	(b) (4)	USP/NF		
Magnesium stearate		USP/NF		
(b) (4)				
Empty hard gelatin capsule, size 4	Capsule shell	In-house ^c		
Total	(b) (4) Capsule Weight			138

3.0 mg Drug Product

<i>Component</i>	<i>Pharmaceutical Function</i>	<i>Quality Standard</i>	<i>Unit Dose Composition</i>	
			<i>(% w/w)</i>	<i>(mg/capsule)</i>
Cariprazine HCl	Drug Substance	In-house ^a		(b) (4)
Pregelatinized starch	(b) (4)	USP/NF		
Magnesium stearate		USP/NF		
(b) (4)				
Empty hard gelatin capsule, size 4	Capsule shell	In-house ^c		
(b) (4)				

4.5 mg Drug Product

<i>Component</i>	<i>Pharmaceutical Function</i>	<i>Quality Standard</i>	<i>Unit Dose Composition</i>	
			<i>(% w/w)</i>	<i>(mg/capsule)</i>
Cariprazine HCl	Drug Substance	In-house ^a		(b) (4)
Pregelatinized starch	(b) (4)	USP/NF		
Magnesium stearate		USP/NF		
(b) (4)				
Empty hard gelatin capsule, size 4	Capsule shell	In-house ^c		
(b) (4)				

6.0 mg Drug Product

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<i>Component</i>	<i>Pharmaceutical Function</i>	<i>Quality Standard</i>	<i>Unit Dose Composition</i>	
			<i>(% w/w)</i>	<i>(mg/capsule)</i>
Cariprazine HCl	Drug Substance	In-house ^a	(b) (4)	
Pregelatinized starch	(b) (4)	USP/NF		
Magnesium stearate	(b) (4)	USP/NF		
(b) (4)				
Empty hard gelatin capsule, size 3	Capsule shell	In-house ^c	(b) (4)	

(b) (4)

a. Per the Type II DMF for Cariprazine HCl

(b) (4)

Evaluation: *Adequate*

Chemistry Assessment Section

The proposed drug product formulation is comprised of (b) (4) the drug substance, pre gelatinized starch and (b) (4) magnesium stearate. The formulations are qualitatively identical. (b) (4)

The applicant provides an adequate description of the drug product including quantities, functions and appropriate references to quality standards. All excipients used in the manufacture of the drug product are compendial (USP or NF).

P.2.1.1 Drug Substance

The drug substance, cariprazine hydrochloride, is a new molecular entity and therefore has no USP monograph. The drug substance is described as a white to almost white (b) (4) powder with a molecular weight of (b) (4). The drug substance (b) (4) Cariprazine HCl exhibits high solubility in the pH range of 1 to 5.5 (see Table 1 in this review) and exhibits BCS Class 1 behavior. The drug substance has been fully characterized. A complete description of the manufacturing process and all relevant characterization data is contained in DMF 26321.

P.2.1.2 Excipients

The excipients used in the manufacture of the drug product are pregelatinized starch and (b) (4) magnesium stearate. Both excipients are compendial, commonly used in the manufacture of solid oral dosage forms and are approved for oral use in the FDA Inactive Ingredient Guide. Based on a MMD of (b) (4) mg of cariprazine hydrochloride, the maximum amounts of magnesium stearate and pregelatinized starch are (b) (4) mg, respectively. The Inactive Ingredient Guide indicates that the maximum potencies for magnesium stearate and pregelatinized starch in capsule dosage form are 256.4 mg and 365.1 mg, respectively. Thus the amounts of magnesium stearate and pregelatinized starch in the proposed formulation are acceptable and consistent with the agency's current thinking and are therefore acceptable. A summary of the dose compositions for each of the potencies of the drug product is included in Table 18 below which has been reproduced from the application.

Table 18

Ingredient	1.5 mg		3.0 mg		4.5 mg		6.0 mg	
	mg/capsule	% w/w						
Cariprazine HCl								(b) (4)
Pregelatinized Starch, USP/NF								
Magnesium Stearate, USP/NF								
Hard Gelatin Capsule								
Total								(b) (4)

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The compatibility of the excipients were evaluated over 4 weeks under ICH accelerated conditions at the ratios indicated in the tables below. The results demonstrate that the excipients have no impact on the assay or degradation product growth (see Tables below)

Table 19

Assay Data From Excipient Compatibility Study		
<i>Sample</i>	<i>Total Assay (% Drug Recovery)</i>	
	<i>Initial</i>	<i>4 Weeks at 40°C/75%RH</i>
Control: Cariprazine (RGH-188) HCl (b) (4)	(b) (4)	
Cariprazine (RGH-188) HCl: Starch (b) (4)		
Cariprazine (RGH-188) HCl: Magnesium Stearate, (b) (4)		
Degradation Products Obtained From Excipient Compatibility Study		
<i>Sample</i>	<i>% Degradation Product</i> (b) (4)	
	<i>Initial</i>	<i>4 Weeks at 40°C/75%RH</i>
Control: Cariprazine (RGH-188) HCl (b) (4)	ND ^a	ND
Cariprazine (RGH-188) HCl: Starch (b) (4)	ND	ND
Cariprazine (RGH-188) HCl: Magnesium Stearate, (b) (4)	ND	ND

^a ND ≤ (b) (4) %

P.2.2 Drug Product

P.2.2.1 Formulation Development

The quality target product profile (QTPP) and the critical quality attributes (CQA) for the drug product are included in the tables below which have been reproduced from the application. The applicant identifies appearance, assay, content uniformity, degradation products, drug release, and microbial limits as the drug product quality attributes. Of these attributes, assay, content uniformity, degradation products and dissolution are the drug product quality attributes that will be investigated as these attributes were considered a high risk in the initial risk assessment and are likely to impact the quality of the drug product.

Table 20: Target Product Profile

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(b) (4)

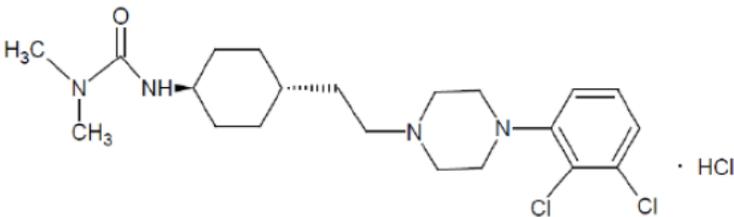
P.2.2.2 *Overages*

The applicant indicates that there are no overages of used in this formulation.

P.2.2.3 *Physicochemical and Biological Properties*

The applicant notes the physicochemical properties of the drug substance are included in the table below and that the critical parameters of the drug product are challenged and controlled through the test included in the drug product specifications.

Chemistry Assessment Section

Structural formula:	
Chemical name (IUPAC nomenclature):	<i>trans</i> -N-(4-[2-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-ethyl]-cyclohexyl)-N',N'-dimethylurea hydrochloride
Molecular formula:	C ₂₁ H ₃₂ Cl ₂ N ₄ O • HCl
Relative molecular mass:	463.87 (Hydrochloride salt) 427.41 (Free base)
Description:	Cariprazine HCl is a white to almost white (b) (4) powder.
Hygroscopicity:	Cariprazine HCl is non-hygroscopic.
BCS Classification:	Class 2 (low solubility, high permeability)
log P:	(b) (4)
Particle size distribution:	D ₁₀ not more than (b) (4) μm D ₅₀ not more than μm D ₉₀ not more than μm
"Apparent" pKa:	8.182 ± 0.023
pH:	4.8 (b) (4)
Melting point:	(b) (4)

P.2.3 Manufacturing Process Development

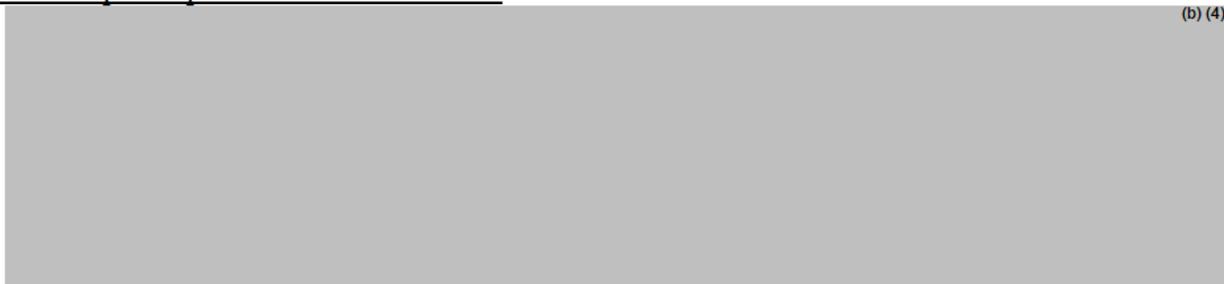
The drug product manufacturing process is

(b) (4)

(b) (4)

Chemistry Assessment Section

The development process activities include:



(b) (4)

The applicant indicates that a QbD approach was used in the development of the manufacturing process. The development strategy was based on developing a process understanding of Cariprazine capsules, risk identification and risk ranking and the development of a design space. The critical quality attributes are included below in Table 26 which has been reproduced from the application.

Table 26

<i>Drug Product Quality Attributes</i>	<i>Target</i>	<i>Justification</i>
Drug Substance Solid State Form	No change in solid state form	Change in solid state form may affect efficacy.
Appearance	No visual defects observed. Color and shape acceptable	Appearance provides indication of capsule integrity and therefore, suitability of drug product.
Identification	Positive for the cariprazine	Identification is critical for safety and efficacy.
Assay	100% of label claim	Variability in assay may affect safety and efficacy.
Content Uniformity	Conforms to Current USP Chapter < 905 > for Uniformity of Dosage Units	Variability in content uniformity may affect safety and efficacy.
Degradation Products	(b) (4) Unspecified (each) ≤ (b) (4) % Total ≤ (b) (4) %	The limit of degradation products is critical for the drug safety and is governed by ICH Q3B.
Dissolution	(b) (4) % (Q) at (b) (4) minutes.	Drug dissolution is an important characteristic of IR dosage form.
(b) (4)		
Microbial Limits	Conforms to the Current USP Chapter < 61 > and Chapter < 62 >	Non-compliance with microbial limits may impact patient safety.

P.2.4 Container Closure System

The applicant describes three primary container closure systems for the drug product:

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- 60-cc square, wide-mouth, white, HDPE bottle and 33-mm, (b) (4) cap
- 120-cc square, wide-mouth, white, HDPE bottle and 38-mm, white, (b) (4) cap
- Unit-dose blister packs ((b) (4) film (b) (4) sealed to (b) (4) (b) (4) (b) (4))

Evaluation: The packaging components comply with the applicable FDA indirect food additive regulations (21 CFR 172-178). Review of the stability data demonstrates the suitability of the proposed container closure system for its intended use. Accordingly, the information provided pertaining to the container closure system is adequate to support this application.

P.2.5 Microbiological Attributes

The 1.5, 3.0, 4.5, 6.0, (b) (4) capsules of the drug product are tested for microbial growth at release and on stability according to USP <61> and <62>. The acceptance criteria for the microbiology are included in Table 27 below.

Table 27

<i>Test</i>	<i>Acceptance Criteria</i>		<i>Method</i>
Microbiology^a	Total aerobic microbial count	NMT (b) (4) cfu/g	Current USP/NF Chapter < 61 > and Chapter < 62 >
	Total combined molds and yeasts count	NMT (b) (4) cfu/g	
	<i>Escherichia coli</i>	Absence in (b) (4)g	

a Test for stability evaluation.

Evaluation: The drug product is a solid oral dosage form, as such the requirements for microbial control as defined in ICH Q6A have been met.

P.2.6 Compatibility

The compatibility of the drug product is demonstrated by the stability data. The applicant includes 24 months of long term (25 C/60% RH) and 6 months of accelerated (40 C/75%RH) stability data for the registration stability batches of the drug product. No additional information provided or required for a solid oral dosage form.

P.3 Manufacture

P.3.1 Manufacturers

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<i>Facility Name and Address</i>	<i>Responsibility/Function</i>
Forest Laboratories Ireland, Ltd. Clonshaugh Business and Technology Park Clonshaugh, Dublin 17, Ireland FDA (FEI): 3002806993 FDA (DUNS): 896303588	Drug product manufacturing, release and stability testing Inactive ingredients release testing
Forest Laboratories, Inc. 220 Sea Lane, Farmingdale, NY 11735 FDA (FEI): 1000521508 FDA (DUNS): 932711815	Drug product release and stability testing
(b) (4)	Compendial excipients testing
	Microbiological testing
	Microbiological testing
Forest Pharmaceuticals, Inc. 5000 Brotherton Road, Cincinnati, OH 45209 FDA (FEI): 1523957 FDA (DUNS): 139645477	Drug product packaging (bottle & blister)
(b) (4)	Drug product packaging (bottle & blister)

All sites were submitted to the Office of Compliance in December 2012. (b) (4) and Forest Laboratories of OH were found acceptable based on profile. (b) (4) and Forest Laboratories of Ireland were found acceptable based on the District recommendation. Gedeon Richter, LTD was assigned an inspection. Accordingly, the overall OC recommendation for this application is pending a final recommendation from the drug substance manufacturer.

P.3.2 Batch Formula

The drug product batch formulas are included in Table 28 below which have been reproduced from the application. The typical batch size is (b) (4) kg which corresponds to (b) (4) capsules.

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Table 28

1.5 mg Cariprazine Capsules Batch Formula				
<i>Component</i>	<i>Quality Standard</i>	<i>Manufacturing Stage</i>	<i>Theoretical Weight</i>	
			<i>(% w/w)</i>	<i>(kg/batch)</i>
Cariprazine HCl	In-house ^a	(b) (4)		(b) (4)
Pregelatinized starch	USP/NF			
Magnesium stearate (b) (4)	USP/NF			
Empty hard gelatin capsule, size 4	In-house ^b			
Theoretical Batch Size (b) (4) capsules)				
3.0 mg Cariprazine Capsules Batch Formula				
<i>Component</i>	<i>Quality Standard</i>	<i>Manufacturing Stage</i>	<i>Theoretical Weight</i>	
			<i>(% w/w)</i>	<i>(kg/batch)</i>
Cariprazine HCl	In-house ^a	(b) (4)		(b) (4)
Pregelatinized starch	USP/NF			
Magnesium stearate (b) (4)	USP/NF			
Empty hard gelatin capsule, size 4	In-house ^b			
Theoretical Batch Size (b) (4) capsules)				
4.5 mg Cariprazine Capsules Batch Formula				
<i>Component</i>	<i>Quality Standard</i>	<i>Manufacturing Stage</i>	<i>Theoretical Weight</i>	
			<i>(% w/w)</i>	<i>(kg/batch)</i>
Cariprazine HCl	In-house ^a	(b) (4)		(b) (4)
Pregelatinized starch	USP/NF			
Magnesium stearate (b) (4)	USP/NF			
Empty hard gelatin capsule, size 4	In-house ^b			
Theoretical Batch Size (b) (4) capsules)				
6.0 mg Cariprazine Capsules Batch Formula				

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<i>Component</i>	<i>Quality Standard</i>	<i>Manufacturing Stage</i>	<i>Theoretical Weight</i>	
			<i>(% w/w)</i>	<i>(kg/batch)</i>
Cariprazine HCl	In-house ^a		(b) (4)	
Pregelatinized starch	USP/NF			
Magnesium stearate (b) (4)	USP/NF			
Empty hard gelatin capsule, size 3	In-house ^b			
Theoretical Batch Size (b) (4) capsules)				

a Per the Type II DMF for cariprazine HCl drug substance by Gedeon Richter, Plc.

b (b) (4)

c (b) (4)

Evaluation: adequate

The batch formulas for the 1.5, 3.0, 4.5, 6.0, (b) (4) mg capsules are qualitatively the same. In each case, the batch size remains unchanged and the (b) (4)

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

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(b) (4)

P.3.5 Process Validation and/or Evaluation

The applicant indicates that process validation will be performed upon product launch.

Evaluation: adequate

The applicant's proposal is acceptable because the manufacturing process is (b) (4)

P.4 Control of Excipients

There are no novel excipients used in the manufacture of the drug product. The excipients used in the manufacture of the drug product are pregelatinized starch, magnesium stearate and the capsules. The pregelatinized starch and magnesium stearate (b) (4) are both compendial. The hard gelatin capsules are non-compendial and are (b) (4) sourced. The

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applicant references DMF [REDACTED] (b)(4) for the manufacture and control of these capsules and provides the appropriate corresponding [REDACTED] (b)(4) declarations.

P.4.1 Specifications

The applicant indicates that the compendial excipients will comply with the current USP or NF, tested according to the current USP/NF methods with no additional testing and includes certificates of analyses for one batch of each of these excipients.

The capsules are accepted by the drug product manufacturer based on the manufacturer's certificate of analyses (see sample CoA for 1.5 mg capsules below) and are released based on identification, description, average capsule weight disintegration and microbial limits (see Table 31 below). Because each of the potencies is differentiated by color (and markings) the body and cap composition of each of the capsules will differ based on the components and composition of the colorants.

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CERTIFICATE OF ANALYSIS

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(b) (4)



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Table 32: Size 4 White (b) (4) Capsules Specifications

	Test	Specification
1	Description	White opaque, hard, empty, size 4 capsule, imprinted with (b) (4) 'FL 1.5'.
2	Identification B (for gelatin)	Complies
3	Average Capsule Weight	(b) (4) mg
4	Disintegration Test	NMT (b) (4) minutes
5	Microbial Limits	
	Total Aerobic Plate Count	< (b) (4) CFU/g
	Escherichia coli	Absent
	Salmonella	Absent

Table 33: Capsule Composition

1.5 mg Capsule		
Body Composition	(b) (4) %	Cap Composition
Titanium dioxide	%	Titanium dioxide
GELATIN	%	GELATIN
3.0 mg Capsule		
Body Composition	%	Cap Composition
Titanium dioxide	%	(b) (4) FD&C Blue 1
GELATIN	%	(b) (4) FD&C Red (b) (4)
		Titanium dioxide
		Yellow iron oxide
		GELATIN
4.5 mg Capsule		
Body Composition	%	Cap Composition
(b) (4) FD&C Blue 1	%	(b) (4) FD&C Blue 1
(b) (4) FD&C Red (b) (4)	%	(b) (4) FD&C Red (b) (4)
Titanium dioxide	%	Titanium dioxide
Yellow iron oxide	%	Yellow iron oxide
GELATIN	%	GELATIN
6.0 mg Capsule		
Body Composition	%	Cap Composition
Titanium dioxide	%	(b) (4) FD&C Blue 1
GELATIN	%	Black iron oxide
		(b) (4) FD&C Red 3
		Titanium dioxide
		GELATIN

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(b) (4)

Comment 4 from Agency's June 5, 2013 Information Request Letter:

Provide the composition the (b) (4) ink used to imprint the capsules.

Summary of Holder's June 14, 2013 Response: The applicant provided the composition of the black ink (see Table 34 below).

Table 34: (b) (4) **Ink Composition**

<i>Component</i>	<i>% W/W</i>	
	<i>NDA Registration Batches</i>	<i>Commercial Batches</i>
		(b) (4)
		(b) (4)

Evaluation: Adequate

P.4.2 Analytical Procedures

The applicant indicates that testing for compendial excipients will comply with USP/NF procedures. The applicant further provides detailed descriptions of the analytical procedures employed to release the capsules and indicates that testing for these non-compendial excipients will comply with USP/NF procedures: identification (USP identification B for gelatin), description (visual), average capsule weight (physical), disintegration (USP <701>) and microbial limits ((USP <61>).

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P.4.3 *Validation of Analytical Procedures*

Compendial excipients are tested according to the current NF or USP as such no validation is included or necessary. The applicant references DMF (b) (4) and DMF (b) (4) for the validation of the analytical procedures for the capsules.

Evaluation: adequate

P.4.4 *Justification of Specifications*

The applicant indicates that the specifications for the compendial excipients were based upon compendial specifications and on the manufacturer's specifications. The non-compendial excipients are accepted based on the manufacturers CoA and tested according to the test outlined in Table X above prior to release. The applicant includes certificates of analyses for each of the inactive ingredients.

Evaluation: adequate

P.4.5 *Excipients of Human or Animal Origin*

The gelatin used in the manufacture of the hard gelatin capsules is of a (b) (4) sourced. The applicant provided the appropriate corresponding (b) (4) declarations.

P.4.6 *Novel Excipients*

There are no novel excipients used in the manufacture of the drug product.

Evaluation: *adequate*

Compendial excipients are tested according to their respective monographs using validated methods. No addition information is required. Non-compendial excipients are accepted based on the manufacturer's certificates of analyses and released based on the specifications included in the table above.

P.5 **Control of Drug Product****P.5.1** *Specification(s)*

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Table 35: Drug Product Specifications

<i>Test^a</i>		<i>Acceptance Criteria</i>	<i>Method</i>
Description^a	1.5 mg	Locked, size # "4" (b)(4) capsule with a (b)(4) "FL 1.5" imprint on the body of the capsule with a (b)(4) (b)(4) Upon opening the capsule, the contents inside should confirm the presence of white to off-white powder.	PRD-TM-ANL-00011
	3.0 mg	Locked, size # "4" (b)(4) (b)(4) body and (b)(4) (b)(4) cap. There is a (b)(4) "FL 3" imprint on the body of the capsule with a (b)(4) Upon opening the capsule, the contents inside should confirm the presence of white to off-white powder.	
	4.5 mg	Locked, size # "4" (b)(4) capsule with a (b)(4) "FL 4.5" imprint on the body of the capsule with a (b)(4) Upon opening the capsule, the contents inside should confirm the presence of white to off-white powder.	
	6.0 mg	Locked, size # "3" capsule with a (b)(4) body and a (b)(4) (b)(4) cap. There is a (b)(4) "FL 6" imprint on the body of the capsule with a (b)(4) Upon opening the capsule, the contents inside should confirm the presence of white to off-white powder.	
		(b)(4)	
Identification^{(b)(4)} (LC-UV)	The retention time of the major peak in the sample corresponds to the retention time of the major peak in the reference solution		PRD-TM-ANL-00132
Identification^{(b)(4)} (UV)	The UV spectrum of the sample conforms to that of the reference standard		PRD-TM-ANL-00890
Content Uniformity	Complies with current USP Chapter < 905 > <i>Uniformity of Dosage Units</i>		PRD-TM-ANL-00132
		(b)(4)	PRD-TM-ANL-00654
Assay^a	(b)(4)% of label claim		PRD-TM-ANL-00132
Dissolution^a	1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg	(b)(4)% (Q) at 15 minutes (b)(4)	PRD-TM-ANL-00701

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Table 35 continued

<i>Test^a</i>	<i>Acceptance Criteria</i>	<i>Method</i>	
Related Substances^a	(b) (4) ≤ (b) (4) %	PRD-TM-ANL-00173	
	≤ %		
	≤ %		
	≤ %	PRD-TM-ANL-00174	
	≤ %		
Total (specified and unspecified)	≤ (b) (4) %	PRD-TM-ANL-00173 and PRD-TM-ANL-00174	
Microbiology^a	Total aerobic microbial count	NMT (b) (4) cfu/g	Current USP/NF Chapter < 61 > and Chapter < 62 >
	Total combined molds and yeasts count	NMT (b) (4) cfu/g	
	<i>Escherichia coli</i>	Absence in (b) (4) g	

a Indicates tests performed on stability.

Evaluation: adequate

The applicant provided acceptance criteria for appearance, identification by LC-UV and UV, content uniformity, assay, related substances, (b) (4), microbial limits, content uniformity and dissolution. The proposed tests included in the drug product specification guarantees the strength, identity and purity of the drug product, are consistent with ICH Q6A and are therefore acceptable. The acceptability of the proposed acceptance criteria will be addressed in section 3.2.P.5.6.

P.5.2 Analytical Procedures

The applicant proposes the following analytical procedures to release the drug product:

Description, identification, content uniformity, (b) (4) assay, dissolution, related substances, microbiology

Description: (b) (4)

Identification, Assay and Content Uniformity by HPLC: (b) (4)

Identification by UV: (b) (4)

Content Uniformity: Determined based on USP Chapter <905> Uniformity of Dosage Units with

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cariprazine content determined using the Identification HPLC method.

Determination of Drug Related Impurities (b) (4)

[Redacted]

Determination of Drug Related Impurities (b) (4)

[Redacted]

Dissolution: (b) (4)

[Redacted]

Determination of (b) (4)

Microbial Limit Testing: Determined in accordance with USP <61> and USP <62> Microbial Limit Test

Evaluation: Adequate – The applicant identified appearance, identification, assay, content uniformity, degradation products, dissolution and microbial limits as critical quality attribute. The proposed methods are appropriate and capable of testing for and controlling the CQA attributes.

P.5.3 Validation of Analytical Procedures

The applicant validated the HPLC methods used for the dissolution, identification, content uniformity, assay and related substances. The validation reports are summarized in the tables below.

Table 41: Dissolution by HPLC

Test	Dissolution of Carprazine (b) (4) Capsules
Method Number	PRD-TM-ANL-00701
Specifications	Q= (b) (4) % at 15 min for 1.5, 3, 4.5 and 6 mg capsules (b) (4)
Method	(b) (4)

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	<p>Dissolution Conditions: Apparatus: USP Apparatus I (baskets) Speed: 100 RPM Media Volume: 500 mL Dissolution Media: Sodium Acetate Buffer pH 5.0 Sampling times: [redacted] ^{(b) (4)} minutes</p> <p>System Suitability Requirements include: %RSD less than or equal to 3.0% for Working Standard</p>
Evaluation	<p>The method validation for the dissolution of the [redacted] ^{(b) (4)} capsules. The acceptability of the method and the discrimination power of the method was evaluated by the biopharmaceutics reviewer and deemed acceptable. The validation of this method included for specificity, linearity, precision, robustness, range and accuracy.</p>
Deficiencies	None

Table 42: Content Uniformity by HPLC

Test	Assay, Identification and Content Uniformity	
Method Number	PRD-TM-ANL-00132	
Specifications	Assay	90.0-110.0%
	Identification	Corresponds to Standard
	Content Uniformity:	Complies with USP <905>
Method	[redacted] ^{(b) (4)}	
Evaluation	<p>The method validation for the assay, content uniformity and identification by <i>HPLC</i> is provided in section 3.2.P.5.3. The validation of this method included [redacted] ^{(b) (4)}</p> <p>[redacted] as well as the following validation characteristics: limit of detection and limit of quantitation, appropriate calculations, specificity, linearity, range, accuracy, precision, robustness and system suitability testing. The applicant included the appropriate calculations and descriptions of sample preparations for each of the aforementioned tests. The method is appropriate for the determination of the</p>	

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	assay, identification and content uniformity.
Deficiencies	None

Table 43: Related Substances by HPLC

Test	(b) (4)
Method Number	
Specifications	
Method	
Evaluation	
Deficiencies	None

Table 44: Related Substances by HPLC

Test	(b) (4)
-------------	---------

Method Number	
Specifications	
Method	
Evaluation	
Deficiencies	None

Evaluation:

The applicant provided the results of analytical procedures validations activities. The methods were validated for specificity, linearity, precision, robustness, range, and accuracy. The applicant established LOQ and LOD for the drug product and the related substances. A summary of the validation procedures are included in the tables above. The results demonstrate that the methods are capable of testing the drug product identity, purity, strength, and performance.

P.5.4 Batch Analyses

The applicant provided batch analyses from three registration lots of each strength of the drug product. The lots were manufactured at the proposed commercial scale ((b)(4) kg) and packaged in the intended container closure systems. Table 45 below which has been reproduced from the application includes the batch numbers, date of manufacture and drug substance batch used.

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Table 45: Summary of NDA Registration Batches

<i>Strength (mg)^a</i>	<i>Drug Product Batch No.^b (Manufacturer Batch No.^c)</i>	<i>Date of Manufacture</i>	<i>Drug Substance Batch No.^d (Manufacturer Batch No.^e)</i>	<i>Packaging Configuration</i>	
1.5	L0004141 (1075220)	(b) (4)	8002587-03 (L8B057F)	60-cc white square HDPE bottle with 33-mm (b) (4) aluminum induction seal cap (Fill Size: 30-count)	
	L0004142 (1077015)		8002587-02 (L8A143A)		
	L0004143 (1075222)		8002587-01 (L8B030F)		
3.0	L0004286 (1079193)		8002587-01 (L8B030F)		120-cc white square HDPE bottle with 38-mm (b) (4) aluminum induction seal cap (Fill Size: 90-count)
	L0004329 (1075225)		8002587-03 (L8B057F)		
	L0004330 (1075224)		8002587-02 (L8A143A)		
4.5	L0004147 (1075227)		8002587-02 (L8A143A)	(b) (4) film sealed to (b) (4) aluminum foil (Fill Size: (b) (4))	
	L0004343 (1075226)		8002587-01 (L8B030F)		
	L0004344 (1075228)		8002587-03 (L8B057F)		
6.0	L0004151 (1075231)		8002587-03 (L8B057F)	(b) (4)	
	L0004384 (1075229)		8002587-02 (L8A143A)		
	L0004385 (1075230)		8002587-01 (L8B030F)		

- a Theoretical batch size = (b) (4) capsules for all strengths.
- b Drug product batch number issued at Forest Research Institute, Inc.
- c Drug product batch number issued at Forest Laboratories Ireland, Limited - drug product manufacturer.
- d Drug substance batch number issued at Forest Laboratories Ireland, Limited - drug product manufacturer.
- e Drug substance batch number issued at Gedeon Richter Plc. - drug substance manufacturer.

Evaluation: Adequate

The applicant manufactured (b) (4) batches (b) (4) of the drug product in April 2010. Of these (b) (4) batches, (b) (4) batches were placed on stability ((b) (4) batches each of the 1.5 (b) (4) and 1 batch of each of the other strengths). All batches were tested according to the acceptance criteria outlined in the drug product specification and all data were within the proposed acceptance criteria. A summary of the data for the CQAs from the (b) (4) batches is as follows: assays ranged from (b) (4) %; dissolution ranged from (b) (4) with at least 1 (b) (4) testing required; (b) (4) % and the total impurities was reported as 0% in all batches.

P.5.5 Characterization of Impurities

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The applicant referenced Gedeon Richter's DMF (DMF 26321) for all information pertaining to the characterization of specified impurities ((b) (4)). DMF 26321 was reviewed in conjunction with this application and is adequate to support the approval of this application. (b) (4) are all specified in the drug substance. As such there are no new impurities identified in the drug product.

P.5.6 Justification of Specification(s)

The specifications provided cover all strengths of Cariprazine Capsules and include: description, identification, assay, (b) (4) drug-related impurities, content uniformity and dissolution.

Description:

The proposed acceptance criterion for each of the potencies reflects the appearance of the drug product when visually examined. The specification includes the capsules size and color as well as marking and contents.

Identification:

The acceptance criterion for the identification by HPLC is "Retention time of the major peak in sample corresponds to the retention time of the major peak in the reference solution". The acceptance criterion for the identification by UV spectrum is "UV spectrum of the sample conforms to that of the reference standard." The specification relies on results from two analytical methods to confirm the identity of Cariprazine in the drug product. The two methods confirm the identity and the proposed specification is appropriate as it is based on results obtained from the indicated methods.

Content Uniformity

The content in each capsule is quantified by HPLC. The acceptance criterion meets USP <905> Content Uniformity requirements and therefore ensures homogeneity in the drug product.

Assay:

The acceptance criterion proposed for the assay for the drug product is 90.0% to 110.0% of label claim. The applicant indicates that this acceptance criterion is "consistent with current industry standards". The applicant does not provide any justification for the acceptance criterion; however, this acceptance criterion is generally accepted for a solid oral dosage form and is in accordance with the ICH guidelines and is therefore acceptable.

(b) (4)

Related Substances:

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The acceptance criteria for the related substances are: (b) (4) NMT (b) (4)%; (b) (4) NMT (b) (4)%, (b) (4), NMT (b) (4)%; individual unspecified, NMT (b) (4)% and total related substances NMT (b) (4)%. The applicant indicates that the limits for the impurities (unspecified, specified, and total) are consistent with the ICH qualifications limit threshold for a product administered orally with a MDD of (b) (4) mg/day.

Dissolution:

In the original submission, the proposed acceptance criterion for the dissolution was $Q = (b) (4)\%$ at (b) (4) minutes. In response to the biopharm comment included in the 74-day letter, the applicant proposed a dissolution acceptance criteria of $Q = (b) (4)\%$ at (b) (4) minutes for all strengths. The applicant indicated that the proposed acceptance criterion is based on release and stability data; however, the biopharm reviewer did not agree with the proposed $Q = (b) (4)\%$ at (b) (4) acceptance criterion. As such, the following comments were conveyed to the applicant in the agency's 05/08/2013 IR letter:

- (b) (4)
- The following acceptance criterion should be implemented for all (b) (4) strengths (1.5, 3, 4.5, 6, (b) (4) mg): $Q = (b) (4)\%$ at 15 min
- Note that the data needed to set dissolution acceptance criterion excludes data from accelerated stability studies. Therefore, the occurrences of (b) (4) are not appropriate since the estimations were made based on data from accelerated storage condition (40/75).

After continued discussion between the biopharm reviewer and the applicant, the applicant accepted the agency's recommendations and the following acceptance criteria were agreed upon:

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
I/100 rpm	Sodium acetate buffer, pH 5.0	500 mL	<ul style="list-style-type: none"> • For 1.5 mg, 3 mg, 4.5 mg and 6 mg: $Q = (b) (4)\%$ at 15 min

Evaluation: adequate

The proposed specifications for the drug product are appropriate and consistent with the agency's current thinking. The identification specification confirms the identity of the drug product via two methods. The Cariprazine content (assay) is consistent with ICH Q6A and generally acceptable for solid oral dosage forms. The related substances (specified and unspecified) are consistent with ICH Q3B. While the acceptance criterion for (b) (4), it is consistent with release and stability data and does not appear to compromise the quality of the drug product. At the onset of the review process the proposed acceptance criterion for the dissolution (i.e. $Q = (b) (4)$ in (b) (4) min) was not acceptable according to the biopharm reviewer Dr. Sandra Suarez. After continued discussions the aforementioned dissolution acceptance criteria (i.e. $Q = (b) (4)\%$ at 15 min for 1.5, 3, 4.5 and 6 mg (b) (4) were agreed upon and deemed acceptable.

P.6 Reference Standards or Materials

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The applicant identifies batch P61005K as the references and provides a certificate of analysis for batch P61005K. The applicant references DMF 26321 for all other relevant CMC information pertaining to the reference standard.

Evaluation: adequate

The applicant reference DMF 26321 for the reference standard. DMF 26321 was reviewed in conjunction with this application and was found adequate to support the approval of this application.

P.7 Container Closure System

Cariprazine capsules packaging configurations are either HDPE bottles (60 or 120cc) or blister strips. The 30 count 60-cc HDPE presentation represents the primary container closure system for the drug product. Both the 60 and 120-cc bottles employ a (b) (4) induction seal cap (33-mm and 38-mm, respectively). The tables below include a summary of the container closure systems based on the intended use and DMF references.

Table 46: Packaging Components

<i>Component Description</i>	<i>Manufacturer</i>	<i>Materials of Construction</i>
60-cc, square, wide-mouth white, HDPE bottle		(b) (4)
33-mm, (b) (4) induction seal cap		
120-cc, square, wide-mouth, white, HDPE bottle		
38-mm, white, (b) (4)		

Table 47: Bottle Container/Closure Components, Manufacturers and DMF References

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<i>Component</i>	<i>Manufacturer</i>	<i>Documentation</i>
60-cc, square, wide-mouth white, HDPE bottle		(b) (4)
120-cc, square, wide-mouth, white, HDPE bottle		
33-mm, (b) (4) induction seal cap		
38-mm, white, (b) (4) cap		

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Table 48: Blister Packaging Components

<i>Component Description</i>	<i>Manufacturer</i>	<i>Materials of Construction</i>
(b) (4) film		
Aluminum foil		
(b) (4) film		
Aluminum foil		

Evaluation: *adequate*

The HDPE bottles and blister packaging described in this application are commonly used container closure systems for solid oral dosage forms. The applicant provides detailed descriptions of the container closure systems and indicates that these systems comply with 21 CFR 177.1520. The applicant includes manufacturers, materials of construction, specifications for materials and parts, certificates of compliance, certificates of analyses, DMF references and the corresponding letters of authorization. All DMF referenced have been previously reviewed for use with solid oral dosage forms. Each of the packaging configurations were evaluated in the long term stability program to establish the drug product shelf life. The applicant has provided sufficient information to support the use of the proposed container closure systems.

P.8 Stability

P.8.1 Stability Summary and Conclusion

The proposed stability protocol for the drug product included a bracketed design (see Table 49 below) in which 3 registration batches (b) (4)

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(b) (4) were placed in the primary stability program in support of approval of Cariprazine Capsules. All samples were manufacture at the proposed commercial scale ((b) (4) capsules) at Forest Laboratories Ireland, Ltd. and packaged in both HDPE bottles (60 and 120 cc) and (b) (4) blisters. The samples were tested for appearance, (b) (4), assay, dissolution, impurities and microbiology. The applicant includes 24 months of data for samples stored under long-term conditions (25°C/65% RH), 6 months of data for samples stored under accelerated conditions (40°C/75% RH) and 12 months of data for samples stored under intermediate conditions (30°C/65% RH). With the exception of one out of specification dissolution results under accelerated conditions, all data was within the prescribed acceptance criteria. There was (b) (4) observed in the assay under long term conditions, (b) (4) under accelerated conditions and the related substances remained virtually unchanged. In addition to the primary stability data, photostability studies were conducted according to ICH guidelines. The results of the photostability studies revealed that the 1.5, 6, (b) (4) capsules are not sensitive to light but the 3 and 4.5 mg capsules which both utilize the green capsule shells show some sensitivity when unpackaged and when packaged in the primary container closure system (adequately protected in secondary packaging).

Overall, there were no significant changes in description, assay, or dissolution performance. (b) (4)

The results show virtually no changes in related impurities. All of the results met the proposed specifications for all capsules strengths. The applicant proposes a storage condition of 25°C with excursions permitted in the range of 15°C – 30°C and a 24 month shelf-life for the drug product. A summary of the data (i.e. storage conditions, batch numbers, packaging, quantity of data) included in the application is summarized in the table below which has be reproduced for the application.

Table 49: Stability Bracketing Design

<i>Strength</i>	<i>1.5 mg</i>			<i>3 mg</i>			<i>4.5 mg</i>		
<i>Batch</i>	<i>L0004141</i>	<i>L0004142</i>	<i>L0004143</i>	<i>L0004286</i>	<i>L0004330</i>	<i>L0004329</i>	<i>L0004343</i>	<i>L0004147</i>	<i>L0004344</i>
Bottles 30-ct	X	X	X	X	O	O	O	X	O
Bottles 90-ct	X	X	X	X	O	O	O	X	O
(b) (4) Blisters	X	X	X	X	O	O	O	X	O
<i>Strength</i>	<i>6 mg</i>			(b) (4)					
<i>Batch</i>	<i>L0004384</i>	<i>L0004385</i>	<i>L0004151</i>						
Bottles 30-ct	O	O	X						
Bottles 90-ct	O	O	X						
(b) (4) Blisters	O	O	X						

X = required testing.

O = optional testing. Samples set up on stability and pulled at designated intervals, but not tested.

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Table 50: Primary Stability Data

Strength	Drug Product Batch No.	Drug Substance Batch No.	Batch Size (Capsules)	Manufacturing Site	Packaging Configuration	Storage Conditions	Time Point (Months)
1.5 mg	L0004141 (Manufacturer batch no. 1075220)	8002587-03 (Manufacturer batch no. L8B057F)	(b) (4)	Forest Laboratories, Ireland, Ltd. Dublin, Ireland	60-cc HDPE bottles (Fill Size: 30-count)	25°C/60% RH	(b) (4)
						40°C/75% RH	
					120-cc HDPE bottles (Fill Size: 90-count)	25°C/60% RH	
						40°C/75% RH	
					Unit-dose (b) (4) blister packs	25°C/60% RH	
						40°C/75% RH	
1.5 mg	L0004142 (Manufacturer batch no. 1077015)	8002587-02 (Manufacturer batch no. L8A143A)	(b) (4)	Forest Laboratories, Ireland, Ltd. Dublin, Ireland	60-cc HDPE bottles (Fill Size: 30-count)	25°C/60% RH	(b) (4)
						40°C/75% RH	
					120-cc HDPE bottles (Fill Size: 90-count)	25°C/60% RH	
						40°C/75% RH	
					Unit-dose (b) (4) blister packs	25°C/60% RH	
						40°C/75% RH	
1.5 mg	L0004143 (Manufacturer batch no. 1075222)	8002587-01 (Manufacturer batch no. L8B030F)	(b) (4)	Forest Laboratories, Ireland, Ltd. Dublin, Ireland	60-cc HDPE bottles (Fill Size: 30-count)	25°C/60% RH	(b) (4)
						40°C/75% RH	
					120-cc HDPE bottles (Fill Size: 90-count)	25°C/60% RH	
						40°C/75% RH	
					Unit-dose (b) (4) blister packs	25°C/60% RH	
						40°C/75% RH	
Strength	Drug Product Batch No.	Drug Substance Batch No.	Batch Size (Capsules)	Manufacturing Site	Packaging Configuration	Storage Conditions	Time Point (Months)
3.0 mg	L0004286 (Manufacturer batch no. 1079193)	8002587-01 (Manufacturer batch no. L8B030F)	(b) (4)	Forest Laboratories, Ireland, Ltd. Dublin, Ireland	60-cc HDPE bottles (Fill Size: 30-count)	25°C/60% RH	(b) (4)
						40°C/75% RH	
					120-cc HDPE bottles (Fill Size: 90-count)	25°C/60% RH	
						40°C/75% RH	
					Unit-dose (b) (4) blister packs	25°C/60% RH	
						40°C/75% RH	
4.5 mg	L0004147 (Manufacturer batch no. 1075227)	8002587-02 (Manufacturer batch no. L8A143A)	(b) (4)	Forest Laboratories, Ireland, Ltd. Dublin, Ireland	60-cc HDPE bottles (Fill Size: 30-count)	25°C/60% RH	(b) (4)
						40°C/75% RH	
					120-cc HDPE bottles (Fill Size: 90-count)	25°C/60% RH	
						40°C/75% RH	
					Unit-dose (b) (4) blister packs	25°C/60% RH	
						40°C/75% RH	
6.0 mg	L0004151 (Manufacturer batch no. 1075231)	8002587-03 (Manufacturer batch no. L8B057F)	(b) (4)	Forest Laboratories, Ireland, Ltd. Dublin, Ireland	60-cc HDPE bottles (Fill Size: 30-count)	25°C/60% RH	(b) (4)
						40°C/75% RH	
					120-cc HDPE bottles (Fill Size: 90-count)	25°C/60% RH	
						40°C/75% RH	
					Unit-dose (b) (4) blister packs	25°C/60% RH	
						40°C/75% RH	

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(b) (4)

P.8.2 Postapproval Stability Protocol and Stability Commitment

The applicant commits to continue long term studies for both packaging configurations through the proposed shelf-life. The applicant commits to placing first three commercial lots batches of the drug product (1.5, 3.0, 4.5, 6.0, (b) (4) mg) in the to-be-marketed container closure systems into the long term stability program. The applicant further commits to place at least one commercial batch into the long term stability program annually. The post-approval stability results will be tabulated and submitted in the annual report and in accordance with 21 CFR 314.81(b)(1)(ii), the applicant commits to reporting any out of specification results in the distributed drug product to the agency.

P.8.3 Stability Data

The stability protocol that was provided for the drug product is summarized in the tables below which have been reproduced from the application. Under long term conditions, samples are scheduled to be tested for description, assay, (b) (4), related substances and dissolution at 0, 3, 6, 9, 12, 18, 24 and 36 months. The stability acceptance criteria are the same as the release acceptance criteria. The applicant included 24 months of long term and 6 months of accelerated data in this application. (b) (4)

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(b) (4)

The long term, intermediate and accelerated data has been reviewed and the results are summarized below.

Table 51: Stability Testing Schedule and Test Attributes

<i>30 and 90 Count HDPE Bottles</i>										
<i>Storage Conditions</i>	<i>Initial</i>	<i>1 M</i>	<i>3 M</i>	<i>6 M</i>	<i>9 M</i>	<i>12 M</i>	<i>15 M^a</i>	<i>18 M</i>	<i>24 M</i>	<i>36 M</i>
25°C/60% RH	X	-	X	X	X	X	X ^a	X	X	X
30°C/65% RH	X	-	O	O	O	O	-	-	-	-
40°C/75% RH	X	X	X	X	-	-	-	-	-	-

X = required testing.
 O = optional testing.
 Test attributes: Description, assay, (b) (4) related substances, dissolution, and microbiology (tested annually).
 (b) (4)

<i>Blister Packaging</i>										
<i>Storage Conditions</i>	<i>Initial</i>	<i>1 M</i>	<i>3 M</i>	<i>6 M</i>	<i>9 M</i>	<i>12 M</i>	<i>18 M</i>	<i>24 M</i>	<i>36 M</i>	
25°C/60% RH	X	-	X	X	X	X	X	X	X	
30°C/65% RH	X	-	(O)	(O)	(O)	(O)	-	-	-	
40°C/75% RH	X	X	X	X	-	-	-	-	-	

X = required testing.
 (O) = optional testing; however, testing activated at 3 months for only (b) (4) due to dissolution out-of-specification (OOS) result at 3 months at 40°C/75% RH.
 Test attributes: Description, assay, (b) (4) related substances, dissolution, and microbiology (tested annually).

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Specification:	[Redacted] ^{(b) (4)}	NMT ^{(b) (4)} %
		NMT %
		NMT %
	Individual Unspecified	NMT %
	Total	NMT %

With the exception of a slight increasing trend in the [Redacted] ^{(b) (4)} under accelerated conditions, there were no stability trends observed for any of the related substances under any storage condition in any packaging configuration for any strength. All results were all well within the proposed acceptance criteria and acceptable. The total impurities ranged from [Redacted] ^{(b) (4)} %.

[Redacted] ^{(b) (4)}

Dissolution

Specification: Q= ^{(b) (4)} % at 15 min for 1.5, 3, 4.5 and 6 mg capsules ^{(b) (4)}

[Redacted] ^{(b) (4)}

The applicant originally proposed a dissolution specification of Q= ^{(b) (4)} at ^{(b) (4)} min. In response to the biopharm comments included in the 74-day letter, and after continued discussions between the agency and the applicant new dissolution specifications (i.e. Q ^{(b) (4)} % at 15 min for 1.5, 3, 4.5 and 6 mg ^{(b) (4)}) were adopted. The results for all strengths were acceptable.

Microbial Limits Tests

Total Aerobic Microbial Count	NMT ^{(b) (4)} cfu/g
Combined Yeast and Molds	NMT ^{(b) (4)} cfu/g
E. coli	Absent in ^{(b) (4)} g

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The results for the microbial limits tests were acceptable across all strengths, packaging configurations and storage conditions. There were no changes noted for any of the samples. The results for the Total Aerobic Microbial Count and Combined Yeast and Molds was less than (b) (4) cfu/g for all samples under all storage conditions and *E. coli* was absent in all batches

Photostability

Photostability studies were conducted on one lot of each strength of the drug product in accordance with ICH guidelines (option 2). The samples were taken from batches L0004142 (1.5 mg), L0004142 (1.5 mg), L0004286 (3 mg), L0004142 (1.5 mg), L0004147 (4.5 mg), L0004151 (6 mg), (b) (4) and tested for description, assay, related substances, dissolution and (b) (4)

Table 53: Photosatbility Protocol

Test	Time Zero	Dark Control	STEP 1	STEP 2	STEP 3
Description	X	X	X	O	O
Assay	X	X	X	O	O
Related Substances	X	X	X	O	O
Dissolution	X	X	X	O	O

(b) (4)

X = required testing, O = optional testing.

The photostability of the drug product was evaluated according to ICH guidelines. The results of the photostability studies samples revealed stability failures for the 3.0 mg and 4.5 mg sample under step 1 and step 2 conditions for the description which suggest that the 1.5 mg, 6 mg, (b) (4) capsules are not light sensitive even when unprotected. The 3.0 and 4.5 mg capsules, which utilize the green capsule shells, are photosensitive even in the primary container closure system. These strengths demonstrated color fading upon exposure to light. Additionally, there was an expected (b) (4) (i.e. (b) (4)%) in the assay noted and (b) (4)

Evaluation: Adequate

The applicant included 24 months of long term and 6 months of accelerated primary stability data for 9 registration batches of the drug product packaged in the 30 count HDPE bottles, 120 count HDPE bottle and (b) (4) blisters using a bracketed stability protocol. In this protocol, the bracket was only applied to the strengths and not the container closure systems. The bracketed protocol included 3 batches each of the highest and lowest strengths and one batch of each of the intermediate strengths. Because the formulations for the strengths are very closely related, the proposed bracketed is consistent with ICH Q1D and is acceptable.

(b) (4) all data were well within the proposed specification limits and there were no unexpected stability trends observed. The only stability

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trend observed was [REDACTED]

(b) (4)

The applicant has request a 24 month shelf-life for all strengths of the drug product. The applicant has demonstrated that the drug product can be adequately stored in all container closure systems (i.e. all data within specifications) at 25° C/60%RH for 24 months when protected from light. The statistical evaluation of the stability data (i.e. linear regression analysis) supports a (b) (4) month expiry for all strengths of the drug product. This prediction (b) (4) the proposed expiry for the drug product by (b) (4) months. Moreover, real-time stability data supports the proposed 24-month expiry for these drug products. Accordingly, a 24-month expriy is appropriate and recommended for the 1.5, 3.0, 6.0, (b) (4) mg drug products.

A APPENDICES**A.1 Facilities and Equipment (biotech only)**

Not applicable

A.2 Adventitious Agents Safety Evaluation

Not applicable

A.3 Novel Excipients

There are no novel excipients in the proposed formulations

R REGIONAL INFORMATION**R1 Executed Batch Records**

The applicant provided executed records for one batch of each strength of the drug product used as primary stability batches. The batches selected were L0004141 (1.5 mg), L0004286 (3.0 mg), L0004147 (4.5 mg), L0004151 (6.0 mg), (b) (4). These batches were manufactured at the commercial scale ((b) (4) kg) and represent the commercial manufacturing process. The information provided is complete and adequate to support this application.

R2 Comparability Protocols

The applicant is proposing the addition of a new drug substance manufacturing site in the comparability protocol. [REDACTED] (b) (4)

The applicant proposes to report this change to the agency in the form of a CBE-30 supplement. [REDACTED] (b) (4)

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Table 54: Comparison of the Manufacturing Equipment for the Dorog, Hungary Site (Site I) and the Budapest, Hungary Site (Site II)

(b) (4)

The applicant indicates that equivalency of the drug substance manufactured at the different sites will be demonstrated by the following:

- Physical Characteristics outlined in Table 56 below for Site I and Site II are comparable

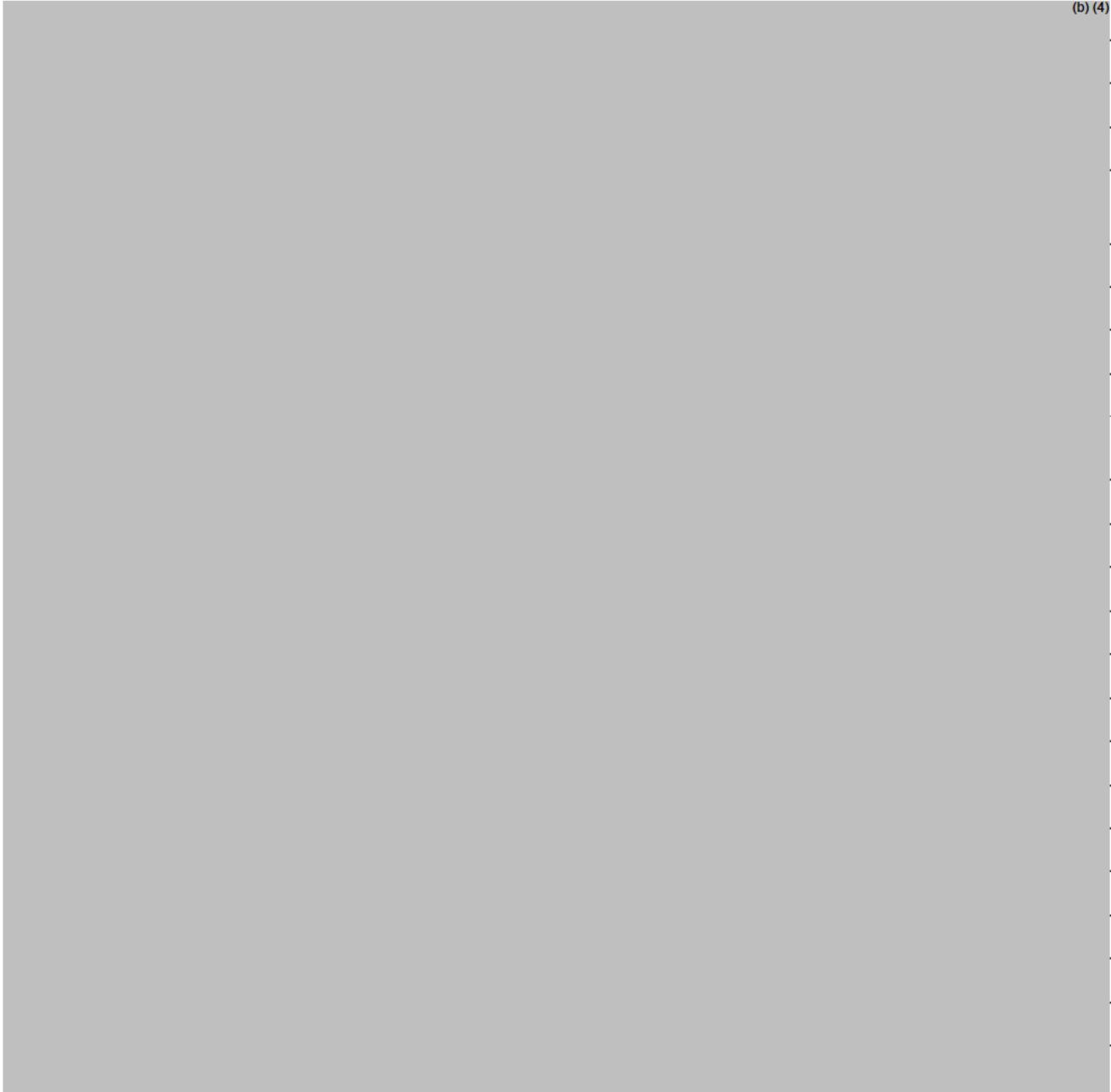
Table 56: Key Physicochemical Characteristics of Cariprazine HCl

Description	White to almost white (b) (4) powder
Solubility	
<i>Solvent</i>	<i>Solubility</i>
Isopropanol	Practically insoluble
Dimethyl formamide	Practically insoluble
Acetone	Very slightly soluble
Acetonitrile	Very slightly soluble
Water	Very slightly soluble
Dichloromethane	Slightly soluble
Ethanol	Slightly soluble
Methanol	Freely soluble
pH	4.8 (b) (4)
pKa	8.182 ± 0.023
logP	4.428 ± 0.043
(b) (4)	(b) (4)
Particle Size Distribution	
D ₁₀	NMT (b) (4) μm
D ₅₀	NMT μm
D ₉₀	NMT μm
Melting Point	(b) (4)
Stereochemistry	Cariprazine HCl molecule has no chiral center
Isomerism	The active substance is trans-isomer
Hygroscopicity	Cariprazine HCl is non-hygroscopic

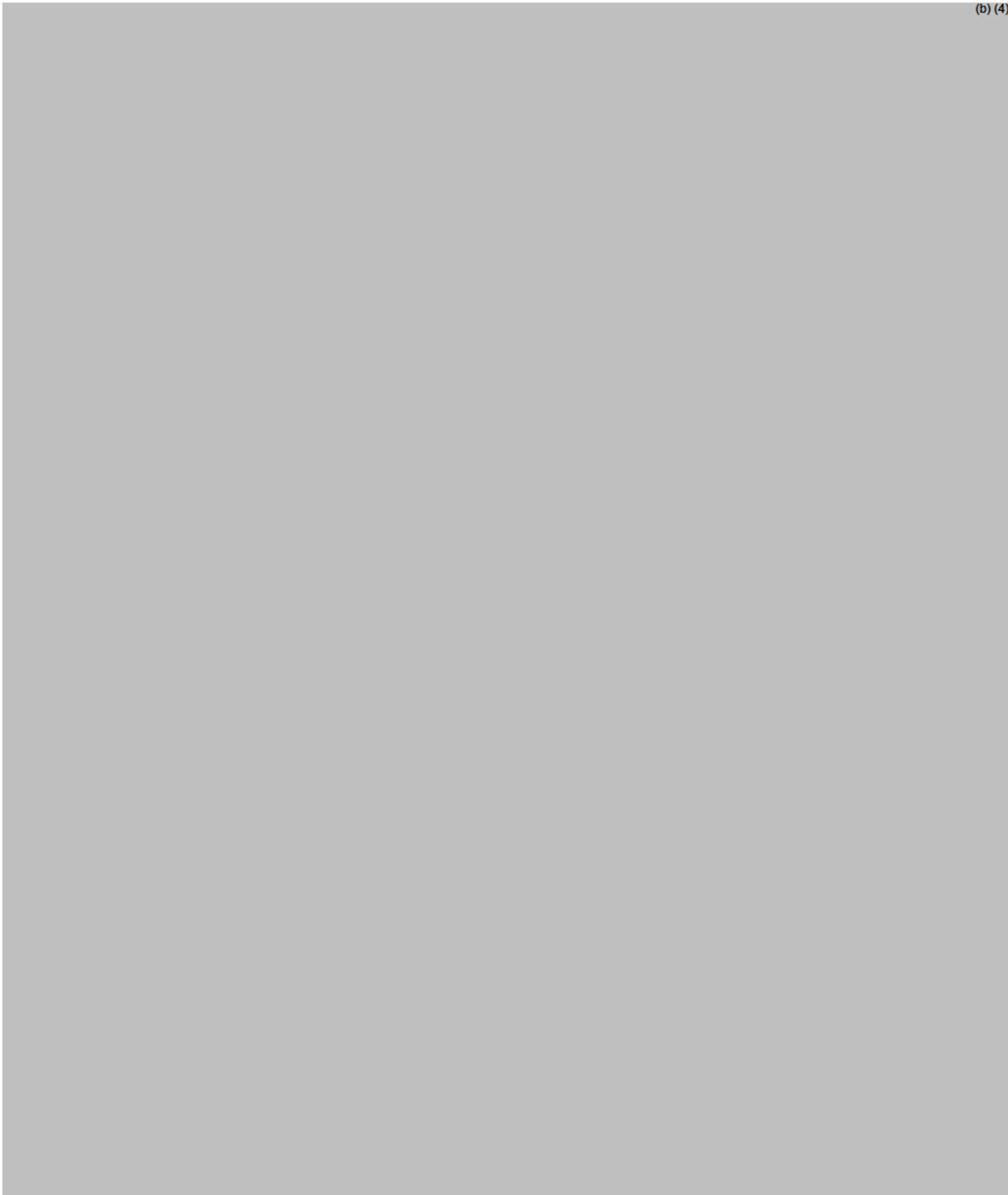
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- The drug substance manufactured at Site II will conform to the approved release specifications for Cariprazine HCl (see Table 5 on page 15 of this review for proposed Cariprazine HCl release specifications)
- Analytical tests and acceptance criteria to control the quality of intermediates (b) (4)

 (see tables 57-60 below).



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(b) (4)

-  ^{(b) (4)} stability data for 3 batches of the drug substance manufactured at the new site (See table 61 below for stability protocol)

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(b) (4)

Comment 7 from Agency's June 5, 2013 Information Request Letter:

Provide the exact address and FEI number for the drug substance manufacturing facility proposed in your comparability protocol.

Summary of Holder's June 14, 2013 Response: The applicant updated the comparability protocol and provided the FEI and DUNS numbers.

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Gedeon Richter Plc.
Gyomroi ut 19-21,
Budapest, Budapest H-1103,
Hungary
FDA (FEI): 3002806761
FDA (DUNS): 644781932

Evaluation: Adequate

Evaluation of Comparability Protocol: *Acceptable*

The comparability protocol was discussed with Dr. Nallaperumal Chidambaram and Dr. Hasmukh Patel of Post Marketing and Dr. Linda Ng of the Office of Compliance. Dr Ng concluded that the proposed post-marketing site of manufacture (Gedeon Richter, Budapest) is currently a synthetic drug manufacturing facility with past FDA inspections that appears to have no CGMP issues or concerns that would preclude the proposed filing category. As such, there were no objections to the filing category request from the compliance perspective. Drs. Chidambaram and Patel both agreed with the proposed filing category. Thus, the proposed changes in the comparability protocol are acceptable.

R3 Methods Validation Package

The methods validation package includes the following information (Table 63):

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<i>Items Description</i>	<i>CTD Module Location</i>
Listing of all samples to be submitted upon request by the FDA	3.2.P.5.4 (all strengths) (Table 3.2.P.5.4.1-1)
Listing of all proposed regulatory specification for the Drug Substance	3.2.S.4.1
Information supporting the integrity of the Reference Standard	3.2.S.5 (Type II DMF by Gedeon Richter, Plc.)
Detailed description of each Method of Analysis	3.2.S.4.2
Information supporting the Suitability Methodology for the Drug Substance	3.2.S.4.3
Composition of the Drug Products	3.2.P.1 (1.5 mg)
	3.2.P.1 (3.0 mg)
	3.2.P.1 (4.5 mg)
	3.2.P.1 (6.0 mg)
	(b) (4)
Listing of all proposed regulatory specification for the Drug Products	3.2.P.5.1 (1.5 mg)
	3.2.P.5.1 (3.0 mg)
	3.2.P.5.1 (4.5 mg)
	3.2.P.5.1 (6.0 mg)
	(b) (4)
Detailed description of each Method of Analysis	3.2.P.5.2 (all strengths)
Information supporting the Suitability Methodology of the Dosage Form	3.2.P.5.3 (all strengths)

In the December 2012 amendment, the applicant indicates that the materials have been provided to the FDA Division of Pharmaceutical Analysis. The methods validation package contained the following samples:

Cariprazine HCl Reference Standard Lot # FMD-RGH-038 (b) (4) g) with COA & MSDS
 Cariprazine HCl Drug Substance Lot # L000006621 (b) (4) g) with COA & MSDS

(b) (4)

Cariprazine Capsules, 1.5mg Lot # Lot # L0004141 (100 ct) with COA
 Cariprazine Capsules, 3.0mg Lot # L0004286 (100 ct) with COA
 Cariprazine Capsules, 4.5mg Lot # L0004147 (100 ct) with COA
 Cariprazine Capsules, 6.0mg Lot # L0004151 (100 ct) with COA

(b) (4)

and the following analytical columns;

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Forest Test Method	Column Dimensions	Column Serial#	Part#	Forest Column#
PRD-TM-ANL-00352 (Assay Drug Substance)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
PRD-TM-ANL-00353 (Impurity Drug Substance)				
PRD-TM-ANL-00132 (Assay Drug Product)				
PRD-TM-ANL-00173 (Impurity Drug Product)				
PRD-TM-ANL-00174 (Impurity Drug Product)				

Evaluation: *adequate*

The applicant includes the lot numbers, certificates of analyses and MSDS sheets were include in the package. Review of the information included in methods validation package is complete and no additional information is needed at this time. The information provided is adequate to support the approval of the pending application.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The figures below illustrate a representative of the proposed bottle and carton label:



4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Each of the carton labels includes a statement such as “Each capsule contains cariprazine HCl equivalent to X mg cariprazine base”. While the statement is acceptable and appropriate, the dose strengths are expressed as Cariprazine base; [REDACTED] (b) (4)

Additionally, photostability data for the 3.0 and 4.5 mg capsules demonstrate that these potencies are sensitive to light; however, the applicant has not included a protect from light statement on the carton or bottle label (see comments below).

The “Description” “Dosage Form and Strengths” and “How Supplied” sections were reviewed. The applicant included the chemical name, molecular formula, molecular weight, [REDACTED] (b) (4) and a physical description of the drug substance in this section. All information contained in the “Description” and “Dosage Form and Strengths” sections were accurate and consistent with the information contained in the application.

Comment 5 from Agency’s June 5, 2013 Information Request Letter:

[REDACTED] (b) (4)

Summary of Holder’s June 14, 2013 Response: The applicant agreed to [REDACTED] (b) (4)

Evaluation: **Adequate**

Comment 6 from Agency’s June 5, 2013 Information Request Letter:

Photostability data for the 3.0 and 4.5 mg capsules demonstrate that these potencies are sensitive to light; however, you have not included a protect from light statement on the package insert, carton or bottle label. Please update these sections to include storage conditions that are consistent with your stability data.

Summary of Holder’s June 14, 2013 Response: The applicant indicated that a “Protect from Light” statement will be added to the packaging and package insert for the 3.0 and 4.5 mg capsules.

Evaluation: **Adequate**

B. Environmental Assessment or Claim of Categorical Exclusion

The applicant claims the “Categorical Exclusion” for the environmental assessment for this NDA in accordance with 21CFR 25.31 (b). Based on 21CFR 25.31(a), a categorical exclusion should be granted as the action taken in this application will increase the use of the active moiety. Additionally, in accordance with 21CFR 25.15 (d), the applicant indicates that no extraordinary conditions exist and the drug substance is not derived from any wild source plant or animal material.

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APPEARS THIS WAY ON ORIGINAL

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

/s/

SHERITA D MCLAMORE
07/18/2013

RAMESH K SOOD
07/18/2013