

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022497Orig1s000

CHEMISTRY REVIEW(S)

Memo

DATE: November 9, 2011
TO: NDA 22-497
FROM: Pei-I Chu, Ph.D.
CMC Reviewer, ONDQA/DPA-1/Branch 1
SUBJECT: **Overall Compliance and CMC Recommendations:**
NDA 22-497, FORFIVOXL (bupropion hydrochloride) 450mg
Tablets

The CDER Office of Compliance (OC) issued an overall "Acceptable" recommendation for NDA 22-497 on November 9, 2011. A copy of the recommendation is attached. From a CMC perspective, all the CMC questions have been properly addressed. The Office of New Drug Quality Assessment recommends **Approval** of the application based on the Office of Compliance recommendation.

ATTACHMENT

NDA 22-497: Overall Acceptable Recommendation from the Office of Compliance

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

| | | | |
|-----------------------|---------------|---|--|
| Application: | NDA 22497/000 | Sponsor: | INTELGENTX |
| Org. Code: | 130 | | 140 PEARL ST STE 100 |
| Priority: | 3S | | BUFFALO, NY 14202 |
| Stamp Date: | 06-APR-2009 | Brand Name: | BUP-450 (BUPROPION HCL)450MG ER ORAL TAB |
| PDUFA Date: | 13-NOV-2011 | Estab. Name: | |
| Action Goal: | | Generic Name: | BUP-450 (BUPROPION HYDROCHLORIDE) 450MGB |
| District Goal: | 08-DEC-2009 | Product Number; Dosage Form; Ingredient; Strengths | 001; TABLET, EXTENDED RELEASE; BUPROPION HYDROCHLORIDE; 450MG |
| FDA Contacts: | T. BOUIE | Project Manager | 301-796-1649 |
| | P. CHU | Review Chemist | 301-796-3887 |
| | C. TELE | Team Leader | 301-796-1762 |

| | | | | | |
|--------------------------------|------------|----------------|-------------|-----------|--------------|
| Overall Recommendation: | ACCEPTABLE | on 09-NOV-2011 | by M. STOCK | (HFD-320) | 301-796-4753 |
| | PENDING | on 02-JUN-2011 | by EES_PROD | | |
| | WITHHOLD | on 06-JAN-2010 | by C. CRUZ | (HFD-323) | 301-796-3254 |
| | ACCEPTABLE | on 18-MAY-2009 | by M. STOCK | (HFD-320) | 301-796-4753 |

| | | | |
|--------------------------|-------------------------|--------------------|---------|
| Establishment: | CFN: | FEI: | (b) (4) |
| | | | (b) (4) |
| DMF No: | | AADA: | |
| Responsibilities: | | OAI Status: | NONE |
| Profile: | | | |
| Last Milestone: | OC RECOMMENDATION | | |
| Milestone Date: | 09-NOV-2011 | | |
| Decision: | ACCEPTABLE | | |
| Reason: | DISTRICT RECOMMENDATION | | |

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

Establishment: CFN: [REDACTED] FEI: (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-JUN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] FEI: 3000241849
PILLAR5 PHARMA INC.
365 MADAWASKA BLVD
ARNPRIOR, ONTARIO, CANADA

DMF No: [REDACTED] **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, EXTENDED RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-SEP-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

PEI-I CHU
11/09/2011

RAMESH K SOOD
11/09/2011

NDA 22-497**Bupropion Hydrochloride
450 mg Extended Release Tablet
(BUP 450 XL)
(Forfivo XL)****Intelgenx Corp.****Pei-I Chu, Ph.D.
Reviewed for Office of New Drug Quality Assessment
DPA1
Division of Psychiatry Drug Products**

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Chemistry Review Data Sheet

1. NDA 22-497
2. REVIEW # 3:
3. REVIEW DATE: September 27, 2011
4. REVIEWER: Pei-I Chu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original

Document Date

31-March-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission

Document Date

04-May- 2011

Quality/Response to Information Request

22-Sep - 2011

7. NAME & ADDRESS OF APPLICANT:

Name: IntelGenx Corp.
Address: 6425 Abrams, Saint-Laurent, Quebec, H4S
1X9, Canada
Representative: Bethany J. Hills, Esq.
Telephone: 716-848-1554

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Forfivo XL
b) Non-Proprietary Name (USAN): Bupropion Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

The reference listed drug product is Wellbutrin XL[®] 150mg Extended-Release tablets, GlaxoSmithKline (GSK), NDA No.21-515

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 450mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

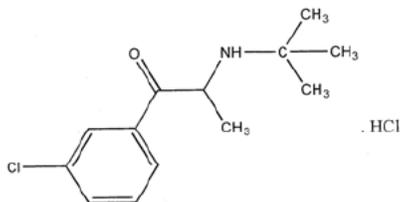
Not a SPOTS product

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

Chemical Name: (±)-2-(tert-butylamino)-3-(4-chlorophenyl)propan-1-one hydrochloride

Molecular Formula : C₁₃H₁₈NO·HCl

Molecular Weight : 276.21



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF# | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|------------|-----------------|-------------------|---------------------|-----------------------|----------------|
| (b) (4) | II | [REDACTED] | (b) (4) | 1 | Adequate | January, 2010 | Drug Substance |
| | IV | | | 3 | Adequate | December, 2009 | Excipient |
| | IV | | | 3 | Adequate | February, 2009 | Excipient |
| | IV | | | 4 | Adequate | January, 1998 | Excipient |
| | III | | | 4 | NA | NA | Package |
| | III | | | 3 | Adequate | June, 2011 | Package |

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 |
|----------|--------------------|---|
| IND | (b) (4) | Bupropion extended release tablet-depressive disorder |

Chemistry Review Data Sheet

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMEN DATION | DATE | REVIEWER |
|--|--|-------------|-----------------|
| Biometrics | n/a | n/a | n/a |
| EES | TBD | | |
| Pharm/Tox | n/a | n/a | n/a |
| Biopharm | Acceptable | 9/22/2011 | Tapash Ghosh |
| LNC | n/a | n/a | n/a |
| Methods Validation | Acceptable | Per review | Pei-I Chu |
| OSE-DMEPA | Acceptable, trade name :Forfivo | 12/28/2009 | Lori Cantin |
| EA | Categorical exclusion granted | Per review | Pei-I Chu |
| Microbiology | n/a | n/a | n/a |

Chemistry Review Section

The Chemistry Review for NDA 22-497**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 22-497 re-submission for bupropion hydrochloride extended release tablet has been reviewed for the chemistry, manufacturing and controls section. An information request letter was sent to the sponsor on September 8, 2011. The sponsor has provided adequate responses to the IR questions on September 22, 2011. The sponsor has also agreed to the dissolution specification proposed by the agency. This NDA will be recommended for approval pending adequate inspection results of the API manufacturing site. The drug product manufacturing and testing sites have been found to be acceptable by Office of Compliance based on profile.

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

None as per this review.

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

Cary Pharmaceuticals, Inc has initially submitted this 505(b)(2) NDA for bupropion hydrochloride 450mg extended release tablet for major depressive disorder. The reference listed drug is Wellbutrin XL[®] (150mg NDA21-515). Wellbutrin XL[®] is not available as a 450mg tablet. The first submission was not approved due to many CMC deficiencies. Intelgenx has taken over NDA 22497 from Cary and filed the resubmission on May 4, 2011.

(b) (4) It contains the following excipients:
hydroxypropyl cellulose, hydrochloric acid, polyvinyl pyrrolidone and polyvinyl acetate blend (b) (4)
polyethylene oxide, stearic acid, colloidal silicon dioxide, and magnesium stearate. (b) (4)
hydroxypropylmethyl cellulose, triacetate, and talc), (b) (4) methacrylic acid
copolymer, polyethylene glycol, titanium dioxide and carboxymethyl cellulose sodium) (b) (4)

(b) (4) all the other ingredients used in the manufacture of the drug product are USP or NF grade. The manufacturing procedures of BUP450XI tablets include (b) (4)

(b) (4) The proposed commercial batch size is (b) (4)
(b) (4) The pivotal stability batches size is (b) (4) The drug product is manufactured by Pillar 5 Pharma Inc. Tablets (30 count) will be packaged in a container closure system consists of a 40 CC HDPE white oblong bottle, a (b) (4) cap fitted with a (b) (4) (heat induction seal) white (b) (4) with liner, a desiccant canister containing 1 g of silica gel, and 0.6 g of (b) (4) coil. A 24M shelf-life has been granted for this drug product.

Bupropion hydrochloride is originally investigated under IND (b) (4) It is a member of the aminoketone class of compound for the treatment of major depressive disorder. Bupropion hydrochloride is a white powder that is soluble in water (450mg bupropion hydrochloride is soluble in approximately (b) (4) of water). The NDA applicant references to DMF (b) (4) for information on bupropion

Chemistry Review Section

hydrochloride (LOA dated April 7, 2011). The drug substance is packaged (b) (4)

(b) (4) DMF (b) (4) has been reviewed by P. Chu and found to be adequate. A (b) (4) re-test date at room temperature storage has been granted for this drug substance during the first review. The DMF holder submitted DMF amendment on April 6, 2011. Up to 60 months of long term stability data was provided in the amendment. The applicant's request to extend the re-test date to (b) (4) has been granted.

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

The labeling states that BUP450XI should be used only in patients who are receiving 300mg once daily of another slow or extended release formulation of bupropion but their depression requires a higher dose of bupropion. These patients have been treated for at least two weeks and tolerate the 300mg dose. The maximum daily dose should not exceed 450mg.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-497 is recommended for approval pending acceptable inspection results of the manufacturing sites from the office of compliance.

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

Pei-I Chu, Ph.D.

B. Endorsement Block

Chemist Name: Pei-I Chu, Ph.D./Date: September 27, 2011
Chemistry Pharmaceutical Lead: Chhagan Tele, Ph.D./Date: September 27, 2011
Chemistry Branch Chief Ramesh Sood, Ph.D./Date: September 27, 2011
Chemistry Project Manager: Teshara Bouie /Date: September 27, 2011

C. CC Block

Orig. NDA-22-497

17 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

PEI-I CHU
09/29/2011

RAMESH K SOOD
09/29/2011

NDA 22-497

**Bupropion Hydrochloride
450 mg Extended Release Tablet
(BUP 450 XL)
(Forfivo XL)**

Intelgenx Corp.

**Pei-I Chu, Ph.D.
Reviewed for Office of New Drug Quality Assessment
DPA1
Division of Psychiatry Drug Products**

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| III. Administrative | 8 |
| A. Reviewer's Signature | 8 |
| B. Endorsement Block | 8 |
| C. CC Block | 8 |
| Chemistry Assessment | 9 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ... | 9 |
| S DRUG SUBSTANCE [Name, Manufacturer] | 9 |
| P DRUG PRODUCT [Name, Dosage form] | 13 |
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| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 | 63 |
| A. Labeling & Package Insert | 63 |
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| C. Establishment Inspection | 70 |
| III. Final CR Questions | 75 |

Chemistry Review Data Sheet

1. NDA 22-497
2. REVIEW # 2:
3. REVIEW DATE: July 25, 2011
4. REVIEWER: Pei-I Chu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N.A.

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Resubmission

Document Date

31-March-2009

04-May- 2011

7. NAME & ADDRESS OF APPLICANT:

Name: IntelGenx Corp.
Address: 6425 Abrams, Saint-Laurent, Quebec, H4S
1X9, Canada
Representative: Bethany J. Hills, Esq.
Telephone: 716-848-1554

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Forfivo XL
b) Non-Proprietary Name (USAN): Bupropion Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

The reference listed drug product is Wilburton XL[®] 150mg Extended-Release tablets, GlaxoSmithKline (GSK), NDA No.21-515

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 450mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

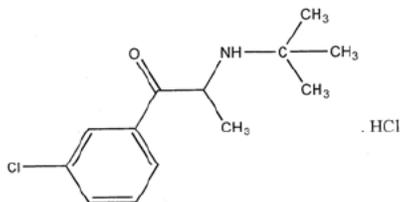
Not a SPOTS product

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

Chemical Name: (±)-2-(tert-butylamino)-3-(4-chlorophenyl)propan-1-one hydrochloride

Molecular Formula : C₁₃H₁₈NO·HCl

Molecular Weight : 276.21



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF# | TYPE | HOLDER | ITEM REFERENCED | CODE1 | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|-------|---------------------|-----------------------|----------------|
| (b) (4) | II | | (b) (4) | 1 | Adequate | January, 2010 | Drug Substance |
| | IV | | | | Adequate | December, 2009 | Excipient |
| | IV | | | 3 | Adequate | February, 2009 | Excipient |
| | IV | | | 3 | Adequate | January, 1998 | Excipient |
| | III | | | 4 | NA | NA | Package |
| | III | | | 3 | Adequate | June, 2011 | Package |
| 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 |
|----------|--------------------|---|
| IND | (b) (4) | Bupropion extended release tablet-depressive disorder |
| | | |
| | | |
| | | |

Chemistry Review Data Sheet

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMEN DATION | DATE | REVIEWER |
|--|--|-------------|-----------------|
| Biometrics | n/a | | --- |
| EES | | --- | --- |
| Pharm/Tox | n/a | ---- | --- |
| Biopharm | TBD | | Tapash Ghosh |
| LNC | n/a | --- | --- |
| Methods Validation | Acceptable | Per review | Pei-I Chu |
| OSE-DMEPA | Acceptable, trade name :Forfivo | 12/28/2009 | Lori Cantin |
| EA | Categorical exclusion granted | Per review | Pei-I Chu |
| Microbiology | n/a | | ---- |

Chemistry Review Section

The Chemistry Review for NDA 22-497

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The approval of NDA 22-497 resubmission for bupropion hydrochloride extended release tablet will be determined based on the response of IR questions dated September 2011. One of the major issues for the non-approval of the original submission (by Cary Pharmaceutical) is for the sponsor to establish a new commercial manufacturing site for this product since the original proposed manufacturer (b) (4) went out of business. Intelgenx has taken over NDA 22497 from Cary and filed the resubmission. A new manufacturing facility has been identified and three pilot batches have been produced in this facility. The new manufacturing sites have been scheduled to be inspected by Office of Compliance.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Cary Pharmaceuticals, Inc has initially submitted this 505(b)(2) NDA for bupropion hydrochloride 450mg extended release tablet for major depressive disorder. The reference listed drug is Wellbutrin XL[®] (150mg NDA21-515). Wellbutrin XL[®] is not available as a 450mg tablet. The first submission was not approved due to many CMC deficiencies. Intelgenx has taken over NDA 22497 from Cary and filed the resubmission on May 4, 2011.

(b) (4) It contains the following excipients:
hydroxypropyl cellulose, hydrochloric acid, polyvinyl pyrrolidone and polyvinyl acetate blend (b) (4)
polyethylene oxide, stearic acid, colloidal silicon dioxide, magnesium stearate. (b) (4)
hydroxypropylmethyl cellulose, triacetate, and talc), (b) (4) methacrylic acid
copolymer, polyethylene glycol, titanium dioxide and carboxymethyl cellulose sodium) (b) (4)

(b) (4) all the other ingredients used in the manufacture of the drug product are USP or NF grade. The manufacturing procedures of BUP450XI tablets include (b) (4)

(b) (4) The proposed commercial batch size is (b) (4)
(b) (4) The pivotal stability batches size is (b) (4) The drug product is manufactured by Pillar 5 Pharma Inc. Tablets (30 count) will be packaged in a container closure system consists of a 40 CC HDPE white oblong bottle, a (b) (4) cap fitted with a (b) (4) (heat induction seal) white (b) (4) with liner, a desiccant canister containing 1 g of silica gel, and 0.6 g of (b) (4) coil.

Bupropion hydrochloride is originally investigated under IND (b) (4) It is a member of the aminoketone class of compound for the treatment of major depressive disorder. Bupropion hydrochloride is a white powder that is soluble in water (450mg bupropion hydrochloride is soluble in approximately (b) (4) of water). The NDA applicant references to DMF (b) (4) for information on bupropion hydrochloride (LOA dated April 7, 2011). The drug substance is packaged (b) (4)

Chemistry Review Section

(b) (4)
DMF (b) (4) has been reviewed by P. Chu and found to be adequate. A (b) (4) re-test date at room temperature storage has been granted for this drug substance during the first review. The DMF holder submitted DMF amendment on April 6, 2011. It includes up to 60 months of long term stability data. Since there is no increase of the drug substance impurity level at this test point, their request to extend the re-test date to (b) (4) has been granted.

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

The labeling states that BUP450XI should be used only in patients who are receiving 300mg once daily of another slow or extended release formulation of bupropion but their depression requires a higher dose of bupropion. These patients have been treated for at least two weeks and tolerate the 300mg dose. The maximum daily dose should not exceed 450mg.

C. Basis for Approvability or Not-Approval Recommendation

The approval of this new drug application (22-497) will be determined pending adequate response of the IR questions.

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

Chemist Name: Pei-I Chu, Ph.D./Date: August 19, 2011
Chemistry Pharmaceutical Lead: Chhagan Tele, Ph.D./Date: August 19, 2011
Chemistry Branch Chief Ramesh Sood, Ph.D./Date: August 19, 2011
Chemistry Project Manager: Teshara Bouie /Date: August 19, 2011

C. CC Block

Orig. NDA-22-497

64 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

PEI-I CHU
08/29/2011

RAMESH K SOOD
09/02/2011

Forfivo XL
(bupropion hydrochloride) extended-release tablets
NDA 22-497

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

Applicant: Cary Pharmaceuticals, Inc.
9903 Windy Hollow Road, Great Falls, VA 22066

Indication: Indicated for the treatment of major depressive disorder.

Presentation: Forfivo XL (bupropion hydrochloride) extended release tablets will be available in 450 mg strength. The commercial presentation for these tablets is a 30 count tablets in a 40 cc, white, HDPE, oblong bottles with (b) (4) white, (b) (4) caps. The bottles will also contain a 2 g desiccant bag and 6.0 g cotton.

EER Status: Withhold, 6-Jan-2010

Consults:
Methods Validation – Revalidation by Agency was not requested.
EA – Categorical exclusion granted under 21 CFR §25.31(c).

Post-Approval Agreements: None

II. Summary of Chemistry Assessments

This application was submitted as a 505(b)(2) NDA. The reference listed drug Wellbutrin XL comes in 150 mg and 300 mg strengths. The reference listed drug is currently approved for major depressive disorder (MDD) and seasonal affective disorder. Cary seeks approval for MDD only.

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

Drug Substance:

Bupropion hydrochloride is a white powder that is soluble in water (450 mg bupropion hydrochloride is soluble in (b) (4) of water). (b) (4)

(b) (4) Bupropion hydrochloride is highly hygroscopic and degrades rapidly when exposed to moisture. The drug substance related CMC information was referenced to DMF (b) (4) held by (b) (4). The DMF was reviewed and found to be adequate to support this NDA. A (b) (4) retest period is

being assigned to bupropion hydrochloride drug substance manufactured by (b) (4)

Conclusion: Acceptable.

Drug product:

The drug product is being developed as extended-release tablets. All excipients used in the manufacturing of the drug product except (b) (4) conform to USP/NF standards.

The manufacturing process consists of (b) (4). The drug product quality is controlled through in-process controls and final product specification. The drug product specification includes tests and acceptance criteria for description, assay (HPLC), identification (IR and HPLC), related substances (HPLC), average tablet weight, (b) (4) content uniformity by weight variation and dissolution. All analytical procedures used for the analysis are appropriately validated. The commercial product will be packaged in HDPE bottles.

Several deficiencies have been identified in the manufacturing process. The major problem with this application from CMC perspective is absence of a commercial drug product manufacturing site. The applicant had used (b) (4) for the manufacturing of registration batches. This company will not be used for the commercial product manufacturing. The applicant has stated that they will be identifying a new commercial manufacturer for their product. Based on this, the applicant will need to submit appropriate CMC information to qualify a commercial drug product manufacturer. Moreover, several other deficiencies related to the current manufacturing process used at (b) (4) product specification and product stability have been identified by the reviewer. The applicant will need to address these deficiencies.

Overall conclusion: The application cannot be recommended for approval in its current form from CMC perspective.

Additional Items: None

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22497

ORIG-1

CARY
PHARMACEUTICA
LS INC

BUP-450 (BUPROPION
HCL)450MG ER ORAL TAB

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/s/

RAMESH K SOOD

01/29/2010

NDA 22-497

**Bupropion Hydrochloride
450 mg Extended Release Tablet
(BUP 450 XL)
(Forfivo XL)**

Cary Pharmaceuticals, Inc

**Pei-I Chu, Ph.D.
Reviewed for Office of New Drug Quality Assessment
DPA1
Division of Psychiatry Drug Products**

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Chemistry Review Data Sheet

1. NDA 22-497
2. REVIEW # 1:
3. REVIEW DATE: January 25, 2010
4. REVIEWER: Pei-I Chu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

31-March-2009

7. NAME & ADDRESS OF APPLICANT:

Address: 9903 Windy Hollow Road
Great Falls, VA 22066

Representative: Douglas D. Cary, R.Ph., M.B.A.

Telephone: 703-759-7460

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Forfivo XL
b) Non-Proprietary Name (USAN): Bupropion Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

The reference listed drug product is Wilburton XL[®] 150mg Extended-Release tablets, GlaxoSmithKline (GSK), NDA No.21-515

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 450mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

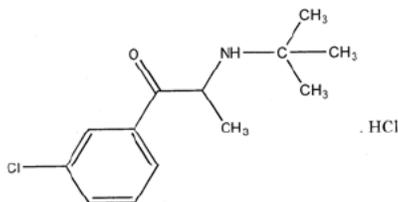
Not a SPOTS product

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

Chemical Name: (±)-2-(tert-butylamino)-3-(4-chlorophenyl)propan-1-one hydrochloride

Molecular Formula : C₁₃H₁₈NO·HCl

Molecular Weight : 276.21



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE1 | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------|---------------------|-----------------------|----------------|
| (b) (4) | II | (b) (4) | (b) (4) | 1 | Adequate | January, 2010 | Drug Substance |
| | IV | | | | Adequate | December, 2009 | Excipient |
| | IV | | | 3 | Adequate | February, 2009 | Excipient |
| | IV | | | 3 | Adequate | January, 1998 | Excipient |

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 |
|----------|--------------------|---|
| IND | (b) (4) | Bupropion extended release tablet-depressive disorder |
| | | |
| | | |
| | | |

Chemistry Review Data Sheet

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMEN DATION | DATE | REVIEWER |
|-------------------------------------|---------------------------------------|------------|------------------|
| Biometrics | n/a | | --- |
| EES | Withheld | 1/06/2010 | Bruce McCullough |
| Pharm/Tox | n/a | ---- | --- |
| Biopharm | Acceptable | 1/25/2010 | Tapash Ghosh |
| LNC | n/a | --- | --- |
| Methods Validation | Acceptable | Per review | Pei-I Chu |
| OSE-DMEPA | Acceptable, trade name :Forfivo | 12/28/2009 | Lori Cantin |
| EA | Categorical exclusion granted | Per review | Pei-I Chu |
| Microbiology | n/a | | ---- |

Chemistry Review Section

The Chemistry Review for NDA 22-497**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 22-497 for bupropion hydrochloride extended release tablets can not be approved in its current form from the CMC standpoint. One of the major issues is the requirement of establishing a new commercial manufacturing site for this product. The original proposed manufacturer (b) (4) went out of business. Cary needs to identify a new contract manufacturer and produce batches to demonstrate that the new facility can produce the drug product with the desirable quality attributes and stability. Additionally, several other issues are listed at the end of the review. Upon satisfactory resolution of the drug product manufacturing deficiencies, the approval status will be re-evaluated.

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

None as per this review.

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

Bupropion hydrochloride was originally investigated under IND (b) (4). It is a member of the aminoketone class of compound for the treatment of major depressive disorder. Bupropion hydrochloride is a white powder that is soluble in water (450mg bupropion hydrochloride is soluble in approximately (b) (4) of water). The NDA applicant references to DMF (b) (4) for information on bupropion hydrochloride (LOA dated Jan 23, 2008). The drug substance is packaged (b) (4)

(b) (4) A (b) (4) re-test date at room temperature storage will be granted for this drug substance.

Cary Pharmaceuticals, Inc has submitted this 505(b)(2) NDA for bupropion hydrochloride extended release tablet for major depressive disorder. The reference listed drug is Wellbutrin XL[®] (150mg NDA21-515). Wellbutrin XL[®] is not available as a 450mg tablet. The drug product is an enterically coated extended release tablet containing 450mg of bupropion hydrochloride (BUP 450 XL). The 450mg tablets contain the following excipients: hydroxypropyl cellulose, hydrochloric acid, polyvinyl pyrrolidone and polyvinyl acetate blend (b) (4) polyethylene oxide, stearic acid, colloidal silicon dioxide, magnesium stearate, (b) (4) hydroxypropylmethyl cellulose, triacetate, and talc, (b) (4) methacrylic acid copolymer, polyethylene glycol, titanium dioxide and carboxymethyl cellulose sodium). (b) (4) all the other ingredients used in the manufacture of the drug product are USP or NF grade. The manufacture of BUP450XL tablets is comprised of (b) (4)

(b) (4) The proposed commercial batch size is (b) (4)
(b) (4) The pivotal stability batches were made with (b) (4)
(b) (4) The drug product was to be manufactured by (b) (4) The tablets will be packaged in 40cc white HDPE oblong bottles (30 count), (b) (4) white (b) (4) cap with (b) (4) liner. There will be a 2g desiccant bag (silica dried gel), and 6.0g of cotton included in each bottle. The applicant has proposed a 24 month expiration date for this product. During the pre-approval inspection for this product, the investigator

Chemistry Review Section

found out that the drug product contract manufacturer ^{(b) (4)} has been out of business. A CR letter concerning the CMC part of the application will be sent out before Feb 6, 2010.

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

The labeling states that BUP450XI should be used only in patients who are receiving 300mg once daily of another slow or extended release formulation of bupropion but their depression requires a higher dose of bupropion. These patients have been treated for at least two weeks and tolerate the 300mg dose. The maximum daily dose should not exceed 450mg.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-497) can not be approved from its current form from the perspective of chemistry, manufacturing, and controls. The deficiencies noted in this review for the drug product needs to be resolved.

III. Administrative

A. Reviewer's Signature

Endorsement Block

Chemist Name:Pei-I Chu, Ph.D./Date: January 12, 2010
Chemisty PAL:Tom Oliver, Ph.D./Date: January 12, 2010
Chemistry Branch Chief Ramesh Sood, Ph.D./Date: January 12, 2010
Chemistry Project Manager Don Henry/Date: January 12, 2010

C. CC Block

Orig. NDA-22-497

68 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|---------------------------------|---|
| NDA-22497 | ORIG-1 | CARY PHARMACEUTICA LS INC | BUP-450 (BUPROPION HCL)450MG ER ORAL TAB |

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/s/

PEI-I CHU
01/28/2010

This NDA can not be approved in its current form from the CMC standpoint.

RAMESH K SOOD
01/28/2010

DATE: November 16, 2009

TO: NDA 22-497 Extended Review Team

FROM: Pei-I Chu, Ph.D.

THROUGH: Christine Moore, Ph.D.

SUBJECT: Considerations for Inspection (PAI) of (b) (4) for NDA 22-497

NDA 22-497 was submitted by Cary Pharmaceutical for BUP-450 XL (bupropion hydrochloride) 450mg oral extended release tablets. Bupropion hydrochloride has a USP monograph. The proposed indication is for treatment of patients with depression. As of 11/16/09, pre-approval inspection was considered not necessary by the Office of Compliance, based on profile.

This memo includes an overview of the drug product manufacturing process and findings from the CMC review. These findings are for consideration by the Office of Compliance and the Office of Regulatory regarding pre-approval inspection.

Overview of the Drug Product Manufacturing Process: The drug product (extended release tablet) is manufactured by a contract manufacturer, (b) (4) using the following steps: (b) (4)

No novel excipients are used. The excipients used are: hydroxypropyl cellulose (b) (4), hydrochloric acid (b) (4), polyethylene oxide (b) (4), stearic acid (b) (4), colloidal silicon dioxide (b) (4), and magnesium stearate (b) (4).

The key critical process parameters for the manufacturing process include: (b) (4)

Based on the information submitted the following concerns are noted:

- The first three stability batches had some dissolution failures. The applicant believed (b) (4) was the problem. As a result, the applicant has modified (b) (4) and manufactured another three batches with this modified (b) (4). 12 month stability data is available for these three lots with the modified (b) (4).
- All six batches (b) (4) placed on stability appear to have been stored in bottles that developed a seal problem when stored under accelerated conditions. Increased impurity levels are observed for the 40%/75% RH stability study after storage for 3 months. The seal problem is currently being

evaluated. The actual problem or corrective actions have not been provided in the application.

- Batches 0704P-01 and 0704P-02 (two out of the six batches made) had problems with

(b) (4)

- Two of the six batches used a mixture of active tablets and placebo tablets (b) (4)

For batch 08039P-01, the operator noticed that an excessive number of placebo tablets broke apart (b) (4). The tablet hardness of both tablets is similar. The cause of the breakage problem is unknown (b) (4).

- An error was noted in batch number 08016P-01. The amount of (b) (4) was initially incorrectly calculated (possibly due to operator error). (b) (4)

however the initial numbers were correct. Even though the error was made, (b) (4)

- When (b) (4) batches (08014P-02 and 08020P-01) were made, there was an insufficient amount of API available at the manufacturing site. As a result, the operator had to re-adjust the batch formula in the batch template to compensate for the lower amount of available API.

The large number of manufacturing irregularities brings to question the ability of the firm to successfully manufacture the drug product under cGMP conditions. The ONDQA reviewer would be happy to meet with the OC and ORA representatives to discuss further, if desired. Furthermore, if an inspection is conducted, the ONDQA reviewer would like an update on any additional accelerated and/or photostability studies.

Pei-I Chu, Ph.D.
Quality Reviewer
301-796-3887

Tom Oliver, Ph.D.
Pharmaceutical Assessment Lead
301-796-1728

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22497

ORIG-1

CARY
PHARMACEUTICA
LS INC

BUP-450 (BUPROPION
HCL)450MG ER ORAL TAB

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/s/

PEI-I CHU
11/16/2009

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-497
Applicant: Cary Pharmaceuticals, Inc.
Letter Date: 31-MAR-09
Stamp Date: 06-APR-09
PDUFA Date: 06-FEB-10
Trademark: BUP 450 XL
Established Name: bupropion hydrochloride
Dosage Form: Extended release tablets (450 mg)
Route of Administration: Oral
Indication: Major Depressive Disorder
Assessed by: Thomas F. Oliver, Ph.D.

Summary

Summary

Cary Pharmaceuticals, Inc. has submitted a 505(b)(2) NDA (paper) for bupropion hydrochloride extended release tablets as a treatment for major depressive disorder. The reference listed drug is Wellbutrin XL® (150 mg and 300 mg; NDA 21-515). Wellbutrin XL® contains bupropion hydrochloride, which is an antidepressant of the aminoketone class and is indicated for the treatment of major depressive disorder (MDD) and seasonal affective disorder. Wellbutrin XL® is not available as a 450 mg strength. Cary plans only to seek the indication of MDD and not the seasonal affective disorder. The applicant developed BUP 450 XL under IND (b)(4). The applicant had a pre-IND meeting (January 30, 2007) with the clinical division to discuss a number of issues including drug product stability plans (bracketing approach, size of batches, and amount of data in original submission). The applicant had an EOP2 meeting (July 14, 2008) with the clinical division to discuss: drug substance and drug product specifications, introduction of ink imprint on commercial tablets, changes to ID/assay/related substances HPLC method, drug product stability protocol, and submission of updated drug product stability data. Minutes for both meetings can be found in DARTS and should be read by the reviewer.

Drug Substance

Bupropion hydrochloride is a white powder that is soluble in water (450 mg bupropion hydrochloride is soluble in (b)(4) of water). (b)(4)

(b)(4) Bupropion hydrochloride is highly hygroscopic and degrades rapidly when exposed to moisture. The NDA applicant references DMF (b)(4) (b)(4) for information on bupropion hydrochloride (LoA dated 23-JAN-08). DMF (b)(4) has not been reviewed (DARTS). Bupropion hydrochloride will be manufactured by (b)(4)

The drug substance will be packaged (b)(4)

Drug Product

BUP 450 XL will be available as 450 mg extended release tablets for the treatment of Major Depressive Disorder. The labeling states that BUP 450 XL should be used only in patients who are receiving 300 mg once daily of another slow or extended release formulation of bupropion, who have been treated for at least two weeks, who tolerate this dose, but whose depression requires a higher dose of extended release of bupropion. The maximum daily dose should not exceed 450 mg. Wellbutrin XL tablets show a lag phase during the first 2 hours of dissolution testing. As a result, BUP 450 XL tablets were designed to contain (b) (4)

(b) (4) and increase the likelihood of bioequivalence. The manufacture of BUP 450 XL tablets is comprised of (b) (4)

(b) (4) The 450 mg tablets contain the following excipients: hydroxypropyl cellulose, hydrochloric acid, polyvinyl pyrrolidone and polyvinyl acetate blend, polyethylene oxide, stearic acid, colloidal silicon dioxide, magnesium stearate, hydroxypropylmethyl cellulose, triacetate, talc, methacrylic acid copolymer, polyethylene glycol, titanium dioxide and carboxymethyl cellulose sodium. The tablets are printed with edible black ink. The drug product is prepared by (b) (4) The proposed commercial batch size is (b) (4) The bupropion hydrochloride extended release tablets will be manufactured by (b) (4)

(b) (4) The tablets will be packaged in 40 cc white HDPE oblong bottles (30 count), (b) (4) white (b) (4) cap with (b) (4) liner, a 2 g desiccant bag (silica dried gel), and 6.0 g of cotton. The container/closure system for commercial product will contain a (b) (4) cap. The applicant has proposed a 24 month expiry.



Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. My recommendation would be for a single reviewer to be assigned to the NDA. Two sites (b) (4) were submitted into EES (18-MAY-09), however, the applicant will need to be asked for the CFN# for the (b) (4) and whether there are any additional testing or packaging sites. In accordance with 21 CFR §25.31, Cary Pharmaceuticals claims a categorical exclusion from the requirement for an Environmental Assessment or Environmental Impact Statement as the Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment will be below 1 ppb. The dissolution should be consulted to the ONDQA dissolution group.

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/s/

Thomas Oliver
5/19/2009 09:29:22 AM
CHEMIST

Ramesh Sood
5/19/2009 03:18:31 PM
CHEMIST