APPLICATION NUMBER:
21-515

CHEMISTRY REVIEW(S)
NDA 21-515

Wellbutrin (bupropion hydrochloride)
Extended Release Tablets

GlaxoSmithKline, Inc

Sherita D. McLamore, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120
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1. NDA 21-515

2. REVIEW # 4

3. REVIEW DATE: 8/29/03

4. REVIEWER: Sherita McLamore, Ph.D.

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7. NAME & ADDRESS OF APPLICANT:

   Name: GlaxoSmithKline
   Address: P.O. Box 7929
            Philadelphia, PA 19101
   Representative: Mary E. Martinson
   Telephone: 919.315.8319

8. DRUG PRODUCT NAME/CODE/TYPE:
a) Proprietary Name: Wellbutrin XL™
b) Non-Proprietary Name / USAN: bupropion hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type: 3
   • Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of major depressive disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   _____SPOTS product – Form Completed
   _X__Not a SPOTS product

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

   Chemical Name: (±)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride
   Molecular Formula: C_{13}H_{16}ClNO •HCl
   Molecular Weight: 276.20

17. RELATED/SUPPORTING DOCUMENTS:
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¹ Action codes for DMF:
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:

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| IND      | 36,571             | Bupropion Hydrochloride -coca
dependence |
| IND      | 45,794             | Bupropion Hydrochloride-smoking cessation |
| NDA      | 18-644             | Wellbutrin® Tablets |
| NDA      | 20-358             | Wellbutrin SR® Tablets |

18. STATUS:
The Chemistry Review for NDA 21-515

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-515 is complete has been approved.

Methods validation will be submitted.

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

N/A

II. Summary of Chemistry Assessments

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

Bupropion Hydrochloride was originally investigated under IND 13,845. Bupropion is a racemate and is a member of the aminoketone class of compounds. Bupropion Hydrochloride is currently approved for use in Wellbutrin SR® Tablets (NDA 20-358) and Wellbutrin Tablets (NDA 18-644). The applicant included very limited information on the drug substance in this application and references for the manufacture and controls of
the drug substance. The drug substance is described as a white crystalline solid that is highly soluble in water and has a bitter taste. Bupropion hydrochloride is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethy) amino]-1-propanone hydrochloride. The molecular formula is C₁₃H₁₈ClNO·HCl and the molecular weight is 276.2. A letter of authorization is provided on page 2 of volume 4.1. There is no information pertaining to the synthesis of the drug substance outlined in this application. The applicant intends to adopt the current USP (effective January 1, 2003) specifications for the drug substance.

The drug product, Wellbutrin XL™ Tablets, is an antidepressant designed for once a day administration. The drug product, Wellbutrin XL™, is a tablet consisting of

Together, the coatings form a that is responsible for the release of the drug substance, bupropion hydrochloride. All ingredients used in the manufacture of the drug product with the exception of Black Ink are either USP or NF grade. The applicant indicates that the drug product will be available in two dosages 150 mg and 300 mg and will be manufactured at the Biovail Lifesciences in Steinbach, CA. The 150 mg tablets are creamy white to pale yellow round tablet imprinted with “Wellbutrin XL 150” in black ink on one side and plain on the other side. The 300 mg tablets are creamy white to pale yellow round tablet imprinted with “Wellbutrin XL 300” in black ink on one side and plain on the other side. The tablets will be packaged in 7 count bottles for physician samples and 30 count bottles for commercial distribution. Both the 30 and 7 count bottles will be packaged with a combination and closed with a child resistant closure.

The applicant proposed the proprietary name Wellbutrin XL™ Tablets for the drug product. The Office of Post-Marketing Drug Risk Assessment (OPDRA) has not posed any objections to the use of this name.

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

Wellbutrin XL™ is being developed for the treatment major depressive disorder. It’s extended release formulation is designed for patients that suffer from MDD. The applicant has provided a confirmatory bioequivalence study comparing Wellbutrin XL™ Tablets with the currently marketed Wellbutrin® Tablets. The applicant indicates that administration should begin with the 150 mg dose and if that dose is well tolerated then the patient should increase to the 300 mg/day target dose. The applicant further indicates that an increase to the maximum daily dose of 450 mg/day may be given as a single dose or divided doses.

The applicant has requested a expiry for the 150 and 300 mg tablets in the 7 and 30 bottles. The applicant provided 6 months of accelerated (40°C/75% RH) stability data together with 12 months of long term (30°C/60% RH) and intermediate (30°C/60% RH) stability data on six batches of the drug product in each of the proposed commercial packages. The applicant updated the dissolution specification from the original submission.
The original dissolution specifications were 2 hours: ___, 4 hours: ___, 8 hours: ___ and 16 hours ___. The new dissolution specifications are 2 hours: ____ 4 hours: ___, 8 hours: ___ and 16 hours ___. Based on the new dissolution specification, there were at the 8 hour time point at 30°C/60% RH and 40°C/75% RH (see stability section of this review). Based on the information provided in this application, the applicant has not provide enough data to support a expiry. The applicant will be granted an 12 month expiry for the 150 and 300 mg tablets in the 7 and 30 bottles.

C. Basis for Approvability or Not-Approval Recommendation
NDA 21-515 is recommended for approval from a CMC standpoint.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block
   SMcLamore/Date
   TOLiver (TL)/Date
   A (PM)/Date

C. CC Block
   Orig. NDA 21-515
   HFD-120/Division File
   HFD-120/DBates
   HFD-120/SMcLamore
   HFD-120/TOLiver

APPEARS THIS WAY ON ORIGINAL
2 Page(s) Withheld

☑ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Sherita McLamore  
8/29/03 01:18:50 PM  
CHEMIST

Thomas Oliver  
8/29/03 01:56:22 PM  
CHEMIST

APPEARS THIS WAY  
ON ORIGINAL
Establishment Evaluation Request

Detail Report

Application: NDA 21515/000

Action Goal: 27-APR-2003

Stamp: 26-AUG-2002

District Goal: 27-APR-2003

Regulatory Due: 03-SEP-2003

Brand Name: WELLBUTRIN XL (BUPROPION)

Applicant: SMITHKLINE BEECHAM CORP DBA GL

Estab. Name: HCL EXTENDED REL

1 FRANKLIN PLAZA

Generic Name: BUPROPION HCL EXTENDED

PHILADELPHIA, PA 19101

RElease TABLETS

Priority: 3S

Dosage Form: (TABLET)

Org Code: 120

Strength: 150 MG AND 300 MG

Application Comment:

FDA Contacts:

D. BATES (HFD-120) 301-594-5536, Project Manager

S. MCLAMORE (HFD-810) 301-594-5359, Review Chemist

T. OLIVER (HFD-810) 301-594-2570, Team Leader

Overall Recommendation: ACCEPTABLE on 31-JUL-2003 by S. FERGUSON (HFD-322) 301-827-9009

ACCEPTABLE on 21-APR-2003 by S. FERGUSON (HFD-322) 301-827-9009

Establishment:

CEN 9615235

FEI 3002806613

BIOVAI LIFESCIENCES

STEINBACH, MANITOBA, CA

DMF No: AADA:

Responsibilities:

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: TCT

OAI Status: NONE

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BASED ON FILE REVIEW
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DISTRICT RECOMMENDATION

Establishment:              

M.F. No:                    
Responsibilities:          
Profile:                    CSN
OAI Status:                 NONE

Instab. Comment:

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DETAILED REPORT

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Establishment: CFN 1033964 FEI 1033964
GLAXO INC
1011 NORTH ARENDELL AVE
ZEBULON, NC 27597

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCT OAI Status: NONE

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INSPECTION

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OC RECOMMENDATION 21-APR-2003 ACCEPTABLE FERGUSONS
DISTRICT RECOMMENDATION

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DUPLICATE MILESTONE FROM FACTS
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Establishment: CFN FEI

Profile: CTL

OAI Status: NONE

Milestone Name | Date | Type | Insp. Date | Decision & Reason | Creator

Appears this way on original
APPEARS THIS WAY
ON ORIGINAL
NDA 21-515

Wellbutrin (bupropion hydrochloride)
Extended Release Tablets

GlaxoSmithKline, Inc

Sherita D. McLamore, Ph.D.
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Chemistry Review Data Sheet

1. NDA 21-515

2. REVIEW # 3

3. REVIEW DATE: 8/15/03

4. REVIEWER: Sherita McLamore, Ph.D.

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7. NAME & ADDRESS OF APPLICANT:

   Name:  GlaxoSmithKline
   One Franklin Plaza
   Address:  P.O. Box 7929
              Philadelphia, PA  19101
   Representative:  Mary E. Martinson
   Telephone:  919.315.8319
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Wellbutrin XL™
   b) Non-Proprietary Name / USAN: bupropion hydrochloride
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 3
      • Submission Priority: 5

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

10. PHARMACOL. CATEGORY: Treatment of major depressive disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_Rx _OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   _____SPOTS product – Form Completed
   _X__Not a SPOTS product

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

   Chemical Name: (±)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride
   Molecular Formula: C_{13}H_{18}ClNO • HCl
   Molecular Weight: 276.20
17. RELATED/SUPPORTING DOCUMENTS:

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

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<td>Bupropion Hydrochloride-smoking cessation</td>
</tr>
<tr>
<td>NDA</td>
<td>18-644</td>
<td>Wellbutrin® Tablets</td>
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The Chemistry Review for NDA 21-515

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-515 is complete and is recommended for approval.

Methods validation will be submitted.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
Bupropion Hydrochloride was originally investigated under IND 13,845. Bupropion is a racemate and is a member of the aminoketone class of compounds. Bupropion Hydrochloride is currently approved for use in Wellbutrin SR® Tablets (NDA 20-358) and Wellbutrin Tablets (NDA 18-644). The applicant included very limited information on the drug substance in this application and references for the manufacture and controls of the drug substance. The drug substance is described as a white crystalline solid that is highly soluble in water and has a bitter taste. Bupropion hydrochloride is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethy) amino]-1-propanone hydrochloride. The molecular formula for is C₁₃H₁₈ClNO.HCl and the molecular weight is 276.2. A letter of authorization is provided on page 2 of volume 4.1. There is no information pertaining to the synthesis of the drug substance outlined in this application. The applicant intends to adopt the current USP (effective January 1, 2003) specifications for the drug substance.

The drug product, Wellbutrin XL™ Tablets, is an antidepressant designed for once a day administration. The drug product, Wellbutrin XL™, is a tablet consisting of a . Together, the coatings form a that is responsible for the release of the drug substance, bupropion hydrochloride. All ingredients used in the manufacture of the drug product with the exception of Black Ink are either USP or NF grade. The applicant indicates that the drug product will be available in two dosages 150 mg and 300 mg and will be manufactured at the Biovail Lifesciences in Steinbach, CA. The 150 mg tablets are creamy white to pale yellow round tablet imprinted with “Wellbutrin XL 150” in black ink on one side and plain on the other side. The 300 mg tablets are creamy white to pale yellow round tablet imprinted with “Wellbutrin XL 300” in black ink on one side and plain on the other side. The tablets will be packaged in 7 count bottles for physician samples and 30 count bottles for commercial distribution. Both the 30 and 7 count bottles will be packaged with a and closed with a child resistant closure.

The applicant proposed the proprietary name Wellbutrin XL™ Tablets for the drug product. The Office of Post-Marketing Drug Risk Assessment (OPDRA) has not posed any objections to the use of this name.

B. Description of How the Drug Product is Intended to be Used
Wellbutrin XL™ is being developed for the treatment major depressive disorder. It's extended release formulation is designed for patients that suffer from MDD. The applicant has provided a confirmatory bioequivalence study comparing Wellbutrin XL™ Tablets with the currently marketed Wellbutrin® Tablets. The applicant indicates that administration should begin with the 150 mg dose and if that dose is well tolerated then the patient should increase to the 300 mg/day target dose. The applicant further indicates that an increase to the maximum daily dose of 450 mg/day may be given as a single dose or divided doses.
The applicant has requested a _____ expiry for the 150 and 300 mg tablets in the 7 and 30 bottles. The applicant provided 6 months of accelerated (40°C/75% RH) stability data together with 12 months of long term (30°C/60% RH) and intermediate (30°C/60% RH) stability data on six _____ batches of the drug product in each of the proposed commercial packages. The applicant updated the dissolution specification from the original submission. The original dissolution specifications were 2 hours: _____, 4 hours: _____, 8 hours: _____, and 16 hours _____ . The new dissolution specifications are 2 hours: _____, 8 hours: _____, and 16 hours _____ . Based on the new dissolution specification, there were _____ at the 8 hour time point at 30°C/60% RH and 40°C/75% RH (see stability section of this review). Based on the information provided in this application, the applicant has not provide enough data to support a _____ expiry. The applicant will be granted an 12 month expiry for the 150 and 300 mg tablets in the 7 and 30 bottles.

C. Basis for Approvability or Not-Approval Recommendation
NDA 21-515 is recommended for approval from a CMC standpoint.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block
SMcLamore/Date
TOliver (TL)/Date
A (PM)/Date

C. CC Block
Orig. NDA 21-515
HFD-120/Division File
HFD-120/DBates
HFD-120/SMcLamore
HFD-120/TOliver
7 Page(s) Withheld

☑ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
8/15/03 02:40:06 PM
CHEMIST

Thomas Oliver
8/15/03 02:49:07 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL
NDA 21-515

Wellbutrin (bupropion hydrochloride)
Extended Release Tablets

GlaxoSmithKline, Inc

Sherita D. McLamore, Ph.D.
Division of Neuropharmacological Drug Products
HFD-120
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# Chemistry Review Data Sheet

1. NDA 21-515

2. REVIEW # 1

3. REVIEW DATE: 5/23/03

4. REVIEWER: Sherita McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

Name: GlaxoSmithKline  
One Franklin Plaza  
Address: P.O. Box 7929  
Philadelphia, PA  19101  
Representative: Mary E. Martinson  
Telephone: 919.315.8319

8. DRUG PRODUCT NAME/CODE/TYPE:
Chemistry Assessment Section

a) Proprietary Name: Wellbutrin XL™
b) Non-Proprietary Name / USAN: bupropion hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type: 3
   • Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of major depressive disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:
   _____SPOTS product – Form Completed
   _X___Not a SPOTS product

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

Chemical Name: (±)-2-(tert-butylamino)-3’-chloropropiophenone hydrochloride
Molecular Formula: C_{13}H_{18}ClNO •HCl
Molecular Weight: 276.20
17. RELATED/SUPPORTING DOCUMENTS:

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

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</table>

The Chemistry Review for NDA 21-515

*The Executive Summary*

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-515 is approvable. The applicant will be sent a list of deficiencies and comments.

Methods validation will be submitted after all CMC deficiencies have been addressed.

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

N/A

II. Summary of Chemistry Assessments

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C. Basis for Approvability or Not-Approval Recommendation
NDA 21-515 is Approvable from a Chemistry standpoint due to chemistry, manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
SMcLamore/Date
TOLiver (TL)/Date
A (PM)/Date

C. CC Block
Orig. NDA 21-515
HFD-120/Division File
HFD-120/DBates
HFD-120/SMcLamore
HFD-120/TOLiver