# CENTER FOR DRUG EVALUATION AND RESEARCH

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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## **Chemistry Review Data Sheet**

- 1. NDA 21-515
- 2. REVIEW # 4
- 3. REVIEW DATE: 8/29/03
- 4. REVIEWER: Sherita McLamore, Ph.D.
- 5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	8/26/02
Amendment	2/11/03
Amendment	4/17/03
CMC Review #1	6/10/03
CMC Review #2	6/10/03
CMC Review #3	8/16/03

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	
Response to Approvable letter	

Document Date 7/03/03

## 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: 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<sub>13</sub>H<sub>18</sub>ClNO •HCl

Molecular Weight: 276.20

17. RELATED/SUPPORTING DOCUMENTS:





## Chemistry Assessment Section

## A. DMFs:

DMF#	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
\$	Type II			1	Adequate	03-25-03	N/A
Λ	Type III	1		1	Adequate	9-26-00	N/A
	Туре Ш	_	] 2	i	Adequate	9-28-00	N/A
	Type III			1	Adequate	8-7-97	N/A
<u> </u>	Type III	<b></b>		1	Adequate	3-2-00	: N/A
	Type III	<u>T</u> ,	_	1	Adequate	3-20-01	N/A
·	Type III	+ <sup>2</sup> · ·	10 _ 2	1	Adequate	06-11-99	N/A

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")

## **B.** Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	28,676	Wellbutrin SR <sup>®</sup> (bupropion hydrochloride)
		Sustained Releases Tablets-antidepressant
IND	13,845	Wellbutrin® (bupropion hydrochloride)
		Tablets-antidepressant
IND	36,571	Bupropion Hydrochloride -cocaine
		dependence
IND	45,794	Bupropion Hydrochloride-smoking cessation
NDA	18-644	Wellbutrin® Tablets
NDA	20-358	Wellbutrin SR® Tablets

## 18. STATUS:

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





## **Chemistry Assessment Section**

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	4/21/03	Office of Compliance
Pharm/Tox	N/A	N/A	N/A
Biopharm	Acceptable pending outcome of DSI inspection	5/12/03	Sally Yasuda
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
DMETS	Acceptable	5/9/03	Jennifer Fan, Pharm.D.
EA	Categorical Exclusion Granted	5/25/05	Sherita McLamore, Ph.D
Microbiology	N/A	N/A	N/A

## 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 Welbutrin 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 1 for the manufacture and controls of





## Chemistry Assessment Section

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  $(\pm)$ -1-(3-chlorophenyl)-2-[(1,1-dimethylethy) amino]-1-propanone hydrochloride. The molecular formula for is  $C_{13}H_{18}ClNO\,HCl$  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<sup>™</sup> Tablets, is an antidepressant designed for once a day

administration. The drug product, Wellbutrin XL<sup>™</sup>, is a I 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

The applicant proposed the proprietary name Wellbutrin XL<sup>™</sup> 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

resistant closure.

Wellbutrin XL<sup>™</sup> 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<sup>™</sup> Tablets with the currently marketed Wellbutrin<sup>®</sup> 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.



## **Chemistry Assessment Section**

The original dissolution specific	cations were 2 hours:	; 4 hours: ; 8 hours:
and 16 hours	The new dissolution specific	ations 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	C/75% RH (see stability section	n of this review). Based on the
information provided in this app	olication, the applicant has not p	provide enough data to support a
expiry. The applicar	nt will be granted an 12 month	expiry for the 150 and 300 mg
tablets in the 7 and 30 bottles.	<u> </u>	<del></del>

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:

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-2003by S. FERGUSON(HFD-322)301-827-9009

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

Establishment:

CFN

9615235

FEI 3002806613

BIOVAIL 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

EM stone Name	Date	Type Insp. Date	e Decision & Reason	Creator
SUBMITTED TO OC	27-SEP-2002			MCLAMORES
SUBMITTED TO DO	30-SEP-2002	GMP		DAMBROGIOJ
DO RECOMMENDATION	07-OCT-2002		ACCEPTABLE	DAMBROGIOJ

BASED ON FILE REVIEW

OC RECOMMENDATION 08-OCT-2002

ACCEPTABLE

DAMBROGIOJ

DISTRICT RECOMMENDATION

Establishment:

OMF No:

AADA:

Responsibilities:

Profile:

CSN

· OAI Status: NONE

Estab. Comment:

**APPEARS THIS WAY** ON ORIGINAL

#### ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Milestone Name Date Type Insp. Date Decision & Reason Creator MCLAMORES SUBMITTED TO OC 27-SEP-2002 ACCEPTABLE DAMBROGIOJ OC RECOMMENDATION 30-SEP-2002 BASED ON PROFILE

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

£Milestone Name	Date	Туре	Insp. Date	Decision & Reason	Creator
			·		
SUBMITTED TO OC	27-SEP-2002				MCLAMORES
SUBMITTED TO DO	27-SEP-2002	GMP			FERGUSONS
ASSIGNED INSPECTION	T 12-NOV-2002	PS			LANDREWS
INSPECTION SCHEDULE	14-NOV-2002		26-APR-2003		LANDREW1@OR
INSPECTION PERFORME	17-APR-2003		17-APR-2003		LANDREWS
INSPECTION PERFORME	17-APR-2003		17-APR-2003		LANDREW18OR

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

DO RECOMMENDATION 21-APR-2003

ACCEPTABLE

LANDREWS

INSPECTION

INSPECTION CONDUCTED ON 4/15-17/03. NO 483 ISSUED. PROFILE CLASS IS ACCEPTABLE.

ACCEPTABLE FERGUSONS COMMENDATION 21-APR-2003

DISTRICT RECOMMENDATION

DO RECOMMENDATION 31-JUL-2003 ACCEPTABLE

LANDREWS

DUPLICATE MILESTONE FROM FACTS

OC RECOMMENDATION 31-JUL-2003

ACCEPTABLE

FERGUSONS

#### DISTRICT RECOMMENDATION

Establishment: CFN

FEI

OMF No:

AADA:

Responsibilities:

?rofile:

CTL

OAI Status: NONE

EMilestone Name Date

Туре

Insp. Date Decision & Reason Creator

APPEARS THIS WAY ON ORIGINAL

#### ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC

27-SEP-2002

MCLAMORES

OC RECOMMENDATION 30-SEP-2002

ACCEPTABLE

DAMBROGIOJ

BASED ON PROFILE

**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 #3
- 3. REVIEW DATE: 8/15/03
- 4. REVIEWER: Sherita McLamore, Ph.D.
- 5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	8/26/02
Amendment	2/11/03
Amendment	4/17/03
CMC Review #1	6/10/03
CMC Review #2	6/10/03

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to Approvable letter	7/03/03

## 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

## CONTRACTOR OF THE

## **CHEMISTRY REVIEW TEMPLATE**



## **Chemistry Assessment Section**

## 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

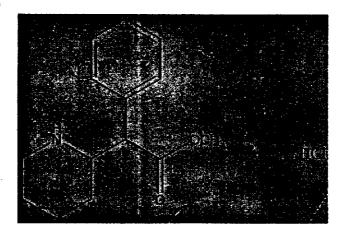
X Not a SPOTS product

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

Chemical Name: (±)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride

Molecular Formula: C13H18CINO •HCl

Molecular Weight: 276.20





## 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF#	ТҮРЕ	HOLDER	ITEM FTERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
:	Туре ІІ	_	· ·	1	Adequate	03-25-03	N/A
	Туре III	1		1	Adequate	9-26-00	N/A
	Type III			1	Adequate	9-28-00	5 N/A
	Type III Type III	_		1	Adequate	8-7-97	N/A
	турс пт	<b>.</b>	<u> </u>	1	Adequate	3-2-00	N/A
<u> </u>	Type III	<u> </u>		1	Adequate	3-20-01	N/A
سان د	Type III	1 C DICE TIL		1	Adequate	06-11-99	N/A

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")

## **B.** Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	28,676	Wellbutrin SR® (bupropion hydrochloride) Sustained Releases Tablets-antidepressant
IND	13,845	Wellbutrin® (bupropion hydrochloride) Tablets-antidepressant
IND	36,571	Bupropion Hydrochloride -cocaine dependence
IND	45,794	Bupropion Hydrochloride-smoking cessation
NDA	18-644	Wellbutrin® Tablets

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





## **Chemistry Assessment Section**

NDA	20-358	Wellbutrin SR® Tablets
INDA	20 330	
l .		

## 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	4/21/03	Office of Compliance
Pharm/Tox	N/A	N/A	N/A
Biopharm	Acceptable pending outcome of DSI inspection	5/12/03	Sally Yasuda
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
DMETS	Acceptable	5/9/03	Jennifer Fan, Pharm.D.
EA	Categorical Exclusion Granted	5/25/05	Sherita McLamore, Ph.D
Microbiology	N/A	N/A	N/A

## 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)



## **Chemistry Assessment Section**

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 Welbutrin 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 C<sub>13</sub>H<sub>18</sub>ClNO 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<sup>™</sup> Tablets, is an antidepressant designed for once a day administration. The drug product, Wellbutrin XL<sup>™</sup>, is a tablet consisting of Fogether, 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 child and closed with a with a resistant closure.

The applicant proposed the proprietary name Wellbutrin XL<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> Tablets with the currently marketed Wellbutrin<sup>®</sup> 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.



## **Chemistry Assessment Section**

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:
hours: , and 16 hours Based on the new dissolution
specification, there were s 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

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/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

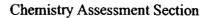
## CHEMISTRY REVIEW TEMPI

**Chemistry Assessment Section** 

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## MISTRY REVIEW TEMPL



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## ISTRY REVIEW TEMP

**Chemistry Assessment Section** 

## **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:

Previous Documents

**Document Date** 

None

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	8/26/02
Amendment	2/11/03
Amendment	4/17/03

## 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:

## STRY REVIEW TEN

## **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

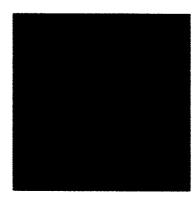
X Not a SPOTS product

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

Chemical Name: (±)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride

Molecular Formula: C<sub>13</sub>H<sub>18</sub>ClNO •HCl

Molecular Weight: 276.20



## MISTRY REVIEW TEM

## **Chemistry Assessment Section**

## 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF#	ТҮРЕ	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	Туре П			1	Adequate	03-25-03	N/A
	Type III	_		1	Adequate	9-26-00	N/A
	Type III			1	Adequate	9-28-00	N/A
	Type III	<del>-</del> -		1	Adequate	8-7-97	N/A
	Type III	_		1	Adequate	3-2-00	N/A
	Type III	<u>,</u>		1	Adequate	3-20-01	N/A
	Type III	des fee DME Tele		11	Adequate	06-11-99	N/A

<sup>1</sup> 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")

#### **B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION	
IND	28,676	Wellbutrin SR® (bupropion hydrochloride)	
		Sustained Releases Tablets-antidepressant	
IND	13,845	Wellbutrin (bupropion hydrochloride)	
		Tablets-antidepressant	
IND	36,571	Bupropion Hydrochloride -cocaine	
		dependence	
IND	45,794	Bupropion Hydrochloride-smoking cessation	
NDA	18-644	Wellbutrin® Tablets	
NDA	20-358	Wellbutrin SR® Tablets	

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

## 18. STATUS:

## **ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	4/21/03	Office of Compliance
Pharm/Tox	N/A	N/A	N/A
Biopharm Acceptable pending outcome of DSI inspection		5/12/03	Sally Yasuda
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
DMETS	Acceptable	5/9/03	Jennifer Fan, Pharm.D.
EA	Categorical Exclusion Granted	5/25/05	Sherita McLamore, Ph.D
Microbiology	N/A	N/A	N/A

## 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 been 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

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

## MEMISTRY REVIEW TEMPL

## **Chemistry Assessment Section**

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 Welbutrin SR® Tablets (NDA 20-358) and Wellbutrin The applicant included very limited information on the drug Tablets (NDA 18-644). for the substance in this application and references 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. hydrochloride is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethy) amino]-1propanone hydrochloride. The molecular formula for is C<sub>13</sub>H<sub>18</sub>ClNO 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<sup>™</sup> Tablets, is an antidepressant designed for once a day administration. The drug product, Wellbutrin XL<sup>™</sup>, 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

The applicant proposed the proprietary name Wellbutrin XL<sup>™</sup> 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.

and closed with a

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

child resistant closure.

bottles will be packaged with a

Wellbutrin XL<sup>™</sup> 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<sup>™</sup> Tablets with the currently marketed Wellbutrin<sup>®</sup> 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.

## MISTRY REVIEW TEMP

## **Chemistry Assessment Section**

The applicant has requested a expiry for the 150 and 300 mg tablets in the 7 and 30 bottles. The applicant has provided 6 months of accelerated stability data together with 12 months of long term and intermediate stability data on six batches of the drug product in each of the proposed commercial packages. All stability data was within the applicants propose specifications.

## 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