CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-108

CHEMISTRY REVIEW(S)

CMC Memorandum for NDA 22-108

NDA #	22-108
Date:	18 April 2008
Product Name:	Bupropion Hydrobromide XL Tablets, 174 mg, 348 mg and 522 mg
Company Name:	Biovail Laboratories International SRL
Subject:	Expiry for Bupropion Hydrobromide XL Tablets, 522 mg

Background

The 24-month expiration period for Bupropion HBr XL Tablets, 174 mg and 348 mg is granted (as requested by Biovail) considering the proposed dissolution specifications as per OCPB Review dated March 19, 2008, i.e. 2 hours – dissolved, 4 hours – dissolved, 8 hours –NLT dissolved. The expiration date was granted for Bupropion HBr XL Tablets, 522 mg HBr XL Tablets based on the stability data evaluated using the final dissolution specifications proposed by OCPB (refer to the Review #3 by Dr. L. Soldatova, dated April 4, 2008). Biovail provided response (dated April 11, 2008) to the information on the expiration date for Bupropion HBr XL Tablets, 522 mg HBr XL Tablets. Additional 15-month dissolution stability data at the shelf life conditions was provided for one batch (#06M128P) of the 522 mg tablets in 90 count bottle, and the F2 analysis for the biobatch #06M126P and for batch #06M128P was provided as well in order to convince the Agency to reconsider expiry for 522 mg HBr XL Tablets. b(4)

Expiry for 522 mg HBr XL Tablets

The 15-month stability data for batch #06M128P (in 90 count bottle) at the shelf life conditions demonstrated that dissolution at 8 hours time point (6 samples, level 1) met the specification of dissolved (range is dissolved). Thus, the out of the specification dissolution data at 12-month for the same batch at 8 hours time point (6 samples, level 1) could be considered as an anomaly, and the downward trend for dissolution of the 522 mg tablets in 90 count bottle is no longer evident (refer to the Review #3 by Dr. L. Soldatova, dated April 4, 2008). However, the dissolution results for 522 mg tablets at the accelerated condition through the 6 months in all package configurations demonstrated the downward trend for % dissolution at 8 hours time point (from initially to dissolved), and some results for 90-count packaged tablets at 8 hours data point are out of the proposed dissolution specification of NLT (Review #2 by Dr. L. Soldatova, dated 2/29/2008). The stability data at the intermediate conditions were not provided, and the Biovail's request of the limit NLT was not accepted by OCPB. Actually, Biovail has accepted the dissolution specifications recommended by OCPB (including the 8-hour limit of dissolved) as stated in the firm's communication dated April 16, 2008. Therefore, only 12-month expiry for 522 mg tablets in all packaging configurations could be granted at this time. b(4)

Acceptance of the expiry for Bupropion HBr XL Tablets, 522 mg

During the Telecon with Biovail on April 16, 2008, the firm has accepted recommendation for the 12-month expiry for 522 mg tablets in all packaging configurations

In addition, the revised bottle labeling for three dosage strengths in three different package configuration (30 count and 90 count bottles) that includes the accepted trade name Aplenzine (submitted to the Agency on April 18, 2008), is acceptable from the standpoint of CMC recommendations. b(4)

b(4)

Lyudmila N. Soldatova, Ph.D.
Review Chemist
OPS/ONDQA/DPA I

cc: HFD-130/ NDA # 22-108
ONDQA/DPAI / RSood
ONDQA/DPAI / LSoldatova
HFD-130/RGrewal
filename: CMC Memo 4.18.2008.doc

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

/s/

Lyudmila Soldatova
4/18/2008 03:45:53 PM
CHEMIST

Ramesh Sood
4/18/2008 03:47:47 PM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-108
From: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 8-Apr-2008
Drug: Bupropion hydrobromide extended-release tablets
Subject: **"Approval"** recommendation for NDA 22-108

Introduction: Bupropion hydrochloride is currently approved for use in an immediate release formulation (Wellbutrin® Tablets; AP 30-DEC-85), a sustained release formulation (Wellbutrin SR® Tablets; AP 04-OCT-96), and an extended release formulation (Wellbutrin XL® Tablets; AP 28-AUG-03). In the current application, bupropion hydrobromide extended release tablets were designed to be bioequivalent to the corresponding strengths of Wellbutrin XL® tablets (bupropion hydrochloride). This product will be available as extended release tablets in 174 mg, 348 mg and 522 mg strengths. The agency issued a "NA" letter dated July 19, 2007. There were several CMC issues identified during the first review cycle. The company responded to these CMC issues in this review cycle. The current reviews #2 and #3 deal with these CMC deficiencies.

Drug Substance: Bupropion hydrobromide is a white to almost white, crystalline powder, soluble in water. The compound contains a chiral center but it is being developed as a racemic mixture. Bupropion hydrobromide is manufactured b(4)
The CMC information related to the drug substance manufacturing is described in
The DMF was reviewed by the CMC reviewer and found adequate following satisfactory resolution of several issues. The applicant has included some relevant drug substance CMC information in the NDA. The quality of the drug substance is assured through appropriate in-process manufacturing controls and through final drug substance specification.

Drug product: The Bupropion HBr extended-release tablets consist of a tablet core surrounded by a controlled release coating. The coating forms a membrane that is responsible for controlling the release of bupropion hydrobromide in vivo. All three strengths of bupropion hydrobromide tablets have the dose proportional tablet core formulation (bupropion, adjusted for tablet weight. The coating formulation consists of ethylcellulose, povidone that controls the b(4)
release of bupropion hydrobromide for a prolonged period of time. The coating solution composition is qualitatively identical for two strengths, 174 mg and 348 mg, and differs for the 522 mg tablets where the carnauba wax in the 522 mg tablets is absent. The quantitative amount of coating applied to each of the tablet strengths is different. The quality of the product is ensured through appropriate in-process controls through manufacturing and the final drug product specification. The final specification includes description, identification by HPLC and IR, uniformity of dosage form, drug release (dissolution), bupropion hydrobromide content, drug related impurities content, moisture content and residual solvents.

The Bupropion hydrobromide extended release tablets, 174 mg, 348 mg, and 522 mg, will be packaged as: 30 ct in white bottles, and 3) b(4)

90 ct in white . bottles, . All b(4)

. The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F). (See USP Controlled Room Temperature).

In this resubmission, Biovail did not accept the dissolution specifications proposed by OCP, and has proposed the following interim dissolution specifications for all dosage strengths (174 mg, 348 mg and 522 mg): 2 hours – NMT dissolved, 4 hours – dissolved, 8 hours – NLT dissolved (Amendment 10/23/2007, Complete Response to AE Letter). However, the OCP does not agree with the proposal and will be asking the company to adopt the following specification: **2 hours – dissolved, 4 hours – dissolved, 8 hours –NLT dissolved.** The CMC reviewer has evaluated the provided stability data based on the OCP recommended dissolution acceptance limits in assigning the product expiration. Based on this evaluation an expiration date of 24-month is being granted for the 174 mg and 348 mg strengths. The stability data for the 522 mg strength tablets showed a downward dissolution trend over time with eventual dissolution failure at 8 hour time point for 12-month samples in one out of three primary batches. Based on these results, an expiration date of is being granted for 522 mg strength. b(4) b(4)

The Office of Compliance has made an overall acceptable recommendation for all the drug substance and drug product manufacturing sites.

Recommended action: The application is recommended as **"Approval"** from CMC perspective.

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/s/

Ramesh Sood
4/8/2008 03:28:38 PM
CHEMIST

4/4/18

CHEMISTRY REVIEW

NDA 22-108

Bupropion Hydrobromide Extended-Release Tablets

Biovail Laboratories International SRL

DIVISION OF PSYCHIATRY DRUG PRODUCTS

Lyudmila N. Soldatova, Ph.D.
DPA I/ONDQA

Review of Chemistry, Manufacturing, and Controls

Table of Contents

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Chemistry Review Data Sheet

1. NDA 22-108

2. REVIEW #3:

3. REVIEW DATE: March 31, 2008

4. REVIEWER: Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	27-SEP-2006
Amendment	13-NOV-2006
Amendment	22-DEC-2006
Amendment	24-MAY-2007
Review #1	06-JUL-2007
Amendment	26-APR-2007
Amendment	06-JUN-2007
Amendment	28-JUN-2007
Amendment	03-JUL-2007
Amendment	10-JUL-2007
Review #2	29-FEB-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	17-MAR-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories International SRL
Keller and Heckman, LLP (U.S. Agent)

Chemistry Review Data Sheet

Address:	Chelston Park, Building 2, Collymore Rock, St. Michael, BHI, Barbados, West Indies U.S. Agent's Address: 1001 G Street, N.W., Suite 500 West Washington, DC 20001
Representative:	John B. Dubeck (U.S. Agent)
Telephone:	202- 434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Bupropion Hydrobromide
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® Tablets, 150 mg and 300 mg, holder GlaxoSmithKlein.

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 174 mg, 348 mg and 522 mg

13. ROUTE OF ADMINISTRATION: Oral

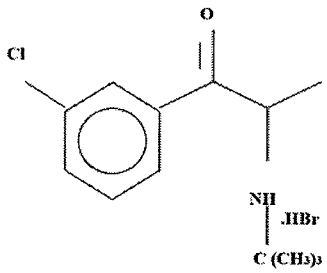
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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 Hydrobromide
Molecular Formula: $C_{13}H_{18}ClNO \cdot HBr$
Molecular Weight: 320.6 g/mole



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate Inadequate	05-16-2007 01-18-2008	
	IV			4	N/A	Adequate information provided in NDA	
	III			3	Adequate	09-28-00 (reviewed by Dr. Klein)	
	III			3	Adequate	09-28-00 (reviewed by Dr. Klein)	
	III			3	Adequate	10-26-2001 (reviewed by Dr. J. Boal)	
	III			3, 4	Adequate	05-15-2007 (reviewed by Drs. W. Wilson and D. Klein). In addition, adequate information provided in review	
	III			1	Adequate	06-08-2007	

b(4)

Chemistry Review Data Sheet

						(reviewed by Dr. L.Soldatova)	

b(4)

[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 relevant 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
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
Clinical	No safety or other clinical concern; approvable/approval recommendation	28-JUN-2007	Robert Levin, MD
EES	Acceptable	07-JUN-2007 22-JAN-2008	Office of Compliance
Pharm/Tox	Pending		Linda Fossom, Ph.D.
OCPB	Dissolution Specifications are proposed	19-MAR-2008	Andre Jackson, Ph.D.
LNC	Receipt of application to USAN name is provided	04-04-2008	
Methods Validation	Acceptable	As per this Review #3	Lyudmila N. Soldatova, Ph.D.
DMETS	Pending		
EA	Acceptable	As per this Review #3	Lyudmila N. Soldatova, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 22-108

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-108 for Bupropion Hydrobromide Extended Release Tablets is recommended APPROVAL from the CMC standpoint. The drug substance and drug product deficiencies were resolved, and the status [redacted] is adequate as per Review #3 dated April 4, 2008. The 24-month expiration period for Bupropion HBr XL Tablets, 174 mg and 348 mg could be granted (as requested by Biovail) considering the proposed dissolution specifications as per OCPB Review dated March 19, 2008. The [redacted] month expiration date could be granted at this time for Bupropion HBr XL Tablets, 522 mg HBr XL Tablets based on the stability data evaluated using the final dissolution specifications proposed by OCPB. Biovail will need to revise the dissolution specification in the drug product specifications according to that proposed by the Agency. b(4)

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)

BACKGROUND

Bupropion hydrobromide extended release Tablets, 174 mg and 348 mg, were designed to be bioequivalent to the corresponding strengths of Wellbutrin XL® tablets, 150 mg and 300 mg (bupropion hydrochloride). Additional higher dosage strength of 522 mg was submitted in this review cycle as well as additional, 18-month stability data for 174 mg and 348 mg tablets, and 12-month stability data for 522 mg tablets. Biovail provided responses to the deficiencies outlined in the Deficiency Letter dated February 26, 2008; all deficiencies have been adequately addressed.

DRUG PRODUCT

Bupropion hydrobromide extended release tablets will be available in three strengths: 174 mg, 348 mg and 522 mg for the treatment of major depressive disorder. The 522 mg/day dose is the highest targeted adult dose. The trade name proposed by Biovail is denied by DMETS, and the name Bupropion HBr XL tablets is used throughout the submission (request to DMETS for trade name [redacted] was submitted on 12-JUL-2007). The Bupropion HBr XL tablets consist of a tablet core surrounded by a controlled release coating. The b(4)

coating. is responsible for controlling the release of bupropion hydrobromide in vivo. Bupropion HBr XL Tablets, 174 mg, 348 mg, and 522 mg, have the same tablet core formulation (bupropion, adjusted for tablet weight. The coating formulation consists of ethylcellulose, povidone that controls the release of bupropion hydrobromide for a prolonged period of time. The coating solution composition is qualitatively identical for two strengths, 174 mg and 348 mg, and differs from the 522 mg tablets by lacking the carnauba wax in the 522 mg tablets. The quantitative amount of coating applied to each of the tablet strengths is different. b(4)

The manufacture of the additional drug product strength, 522 mg drug product consists of the same steps as that for the 174 mg and 348 mg strength, and the same analytical methods were utilized for release and stability resting of the 522 mg tablets.

The release specification for three dosage strengths of Bupropion HBr XL tablets include description, identification by HPLC and IR, uniformity of dosage form, drug release (dissolution), bupropion hydrobromide content, drug related impurities content, moisture content and residual solvents. After revision, the drug product specifications now include a second identification test (method), a specified moisture content limit of NMT and a reduced acceptance criterion . Biovail did not adopt the dissolution specifications proposed by OCPB, and has proposed the interim dissolution specifications for all dosage strengths (174 mg, 348 mg and 522 mg) as follows: 2 hours – NMT dissolved, 4 hours – dissolved, 8 hours –NLT dissolved (Amendment 10/23/2007, Complete Response to AE Letter). **The current proposed by OCPB dissolution specification is as follows: 2 hours – dissolved, 4 hours – dissolved, 8 hours –NLT dissolved.** The three batches of Bupropion HBr XL tablets of each strength, 174 mg, 348 mg and 522 mg were manufactured to-date at the commercial scale at the Biovail Corporation in Steinbach, Manitoba, Canada. The overall Acceptable recommendation from the Office of Compliance was received (June 07, 2007 and January 22, 2008) for drug substance and drug product manufacturing facilities of Bupropion HBr XL tablets (see Attachment 1 for detailed EES report). The batches of drug product tablets of two strengths, 174 mg and 348 mg, were manufactured using one lot of Bupropion HBr drug substance, and different drug substance lot was used for production of 522 mg strength. The release results of the drug substance batch 06PB0102 used to manufacture Bupropion tablets, 174 mg and 348 mg, are very similar to that of the drug substance batch 06PC0188 used to manufacture Bupropion tablets, 522 mg, and to that of the three batches of drug substance presented . The comparison of the release data for batches of 522 mg tablets to that of the 174 mg and 348 mg shows the similarity of all these batches by the results of the tested parameters. The batch results of the 522 mg drug product demonstrated that all data was within the proposed specification. b(4) b(4)

The applicant provided 18-month stability data at 25° C/60% RH and 6-month data at 40° C/75% RH for 3 batches of each 174 mg and 348 mg tablets, and 12-month stability data at 25° C/60% RH and 6-month data at 40° C/75% RH for 3 batches of 522 mg tablets (all data provided for batches packaged in three different package configuration). The 24-month

expiration period for Bupropion HBr XL Tablets, 174 mg and 348 mg could be granted (as requested by Biovail) considering the proposed dissolution specifications as per OCPB Review dated March 19, 2008. The [redacted] expiration date could be granted at this time for Bupropion HBr XL Tablets, 522 mg HBr XL Tablets based on the stability data evaluated using the final dissolution specifications proposed by OCPB. The dissolution data at 8 hours (at 12-month time point) for one out of three tablet batches in 90 counts bottles did not meet the specification of NLT [redacted] dissolved; however, the failed batch has met the limit of NLT [redacted] dissolved at 9-month time point. In addition, the dissolution results at 8 hours time point through 12 months of shelf life storage for all packaging configurations demonstrate a downward trend, and this trend is more pronounced with higher count packaging. b(4)

DRUG SUBSTANCE

The sponsor references Type II DMF [redacted] for information on the drug substance Bupropion Hydrobromide (LoA dated 12-MAY-05). [redacted] is reviewed and found Adequate (Review #3 by Dr. Lyudmila Soldatova, dated 04-APR-2008). The drug substance is manufactured commercially [redacted] [acceptable OC recommendation dated 07-JUN-2006]. Biovail has included a test and limit for particle size distribution, and set limits for bulk and tapped densities in the acceptance drug substance specifications. In addition, Biovail has reduced the specification limit to [redacted] for the potential genotoxic impurity [redacted] in the drug substance specifications; described the HPLC analytical method for detection of this impurity with LOD of [redacted], and provided data that demonstrated the "Below LOD" level of this impurity in five Bupropion HBr batches. b(4)

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

The Bupropion hydrobromide extended release tablets, 174 mg, 348 mg, and 522 mg will be packaged as: [redacted] 30 ct in white [redacted] bottles, and [redacted] 90 ct in white [redacted] bottles [redacted] b(4)

The recommended starting dose should be 174 mg/day as a single daily dose given in the morning. If the 174 mg dose is adequately tolerated, an increase to 522 mg/day, given once daily, can be made as early as day four.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F). (See USP Controlled Room Temperature).

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-108 for Bupropion Hydrobromide Extended Release Tablets is recommended **Approval** from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Renmeet Grewal

C. CC Block

See DFS.

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15 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Lyudmila Soldatova
4/4/2008 04:56:05 PM
CHEMIST

Ramesh Sood
4/4/2008 04:58:16 PM
CHEMIST

2/2/2

CHEMISTRY REVIEW

NDA 22-108

Bupropion Hydrobromide Extended-Release Tablets

Biovail Laboratories International SRL

DIVISION OF PSYCHIATRY DRUG PRODUCTS

Lyudmila N. Soldatova, Ph.D.
DPA I/ONDQA

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-108

2. REVIEW #2:

3. REVIEW DATE: February 20, 2008

4. REVIEWER: Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	27-SEP-2006
Amendment	13-NOV-2006
Amendment	22-DEC-2006
Amendment	24-MAY-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	26-APR-2007
Amendment	06-JUN-2007
Amendment	28-JUN-2007
Amendment	03-JUL-2007
Amendment	10-JUL-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Biovail Laboratories International SRL Keller and Heckman, LLP (U.S. Agent)
Address:	Chelston Park, Building 2, Collymore Rock, St. Michael, BHI, Barbados, West Indies U.S. Agent's Address: 1001 G Street, N.W., Suite 500 West Washington, DC 20001
Representative:	John B. Dubeck (U.S. Agent)

Chemistry Review Data Sheet

Telephone: 202- 434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Bupropion Hydrobromide
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® Tablets, 150 mg and 300 mg, holder GlaxoSmithKlein.

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 174 mg, 348 mg and 522 mg

13. ROUTE OF ADMINISTRATION: Oral

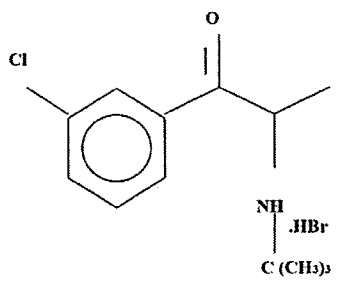
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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 Hydrobromide
Molecular Formula: $C_{13}H_{18}ClNO \cdot HBr$
Molecular Weight: 320.6 g/mole



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate Inadequate	05-16-2007 01-18-2008	
	IV			4	N/A	Adequate information provided in NDA	
	III			3	Adequate	09-28-00 (reviewed by Dr. Klein)	
	III			3	Adequate	09-28-00 (reviewed by Dr. Klein)	b(4)
	III			3	Adequate	10-26-2001 (reviewed by Dr. J. Boal)	
	III			3, 4	Adequate	05-15-2007 (reviewed by Drs. W. Wilson and D. Klein). In addition, adequate information provided in review	
	III			1	Adequate	06-08-2007 (reviewed by Dr. L.Soldatova)	

[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 relevant 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
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
Clinical	No safety or other clinical concern; approvable/approval recommendation	28-JUN-2007	Robert Levin, MD
EES	Acceptable	07-JUN-2007 22-JAN-2008	Office of Compliance
Pharm/Tox	Pending		Linda Fossom, Ph.D.
OCPB	Pending		Andre Jackson, Ph.D.
LNC	USAN is not available		
Methods Validation	Pending	Pending as per this review	Lyudmila N. Soldatova, Ph.D.
DMETS	Pending		
EA	Pending		Lyudmila N. Soldatova, Ph.D.
Microbiology	N/A		

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The Chemistry Review for NDA 22-108

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-108 for Bupropion Hydrobromide Extended Release Tablets is recommended APPROVABLE from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance and drug product deficiencies, and on the adequate status of the DMF . The expiration period for Bupropion HBr XL Tablets, 174 mg and 348 mg could be granted (as requested by Biovail) pending on the final adopted dissolution specifications. The expiration date could not be granted at this time for Bupropion HBr XL Tablets, 522 mg HBr XL Tablets; additional stability data is required. b(4)

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)

BACKGROUND

Bupropion hydrobromide extended release Tablets, 174 mg and 348 mg, were designed to be bioequivalent to the corresponding strengths of Wellbutrin XL® tablets, 150 mg and 300 mg (bupropion hydrochloride). Additional higher dosage strength of 522 mg was submitted in this review cycle as well as additional, 12-month stability data for 174 mg and 348 mg tablets, and 6-month stability data for 522 mg tablets. Biovail provided responses to the deficiencies outlined in the Deficiency Letter dated July 19, 2007; not all deficiencies have been adequately addressed at this time.

DRUG PRODUCT

Bupropion hydrobromide extended release tablets will be available in three strengths: 174 mg, 348 mg and 522 mg for the treatment of major depressive disorder. The 522 mg/day dose is the highest targeted adult dose. The trade name proposed by Biovail is denied by DMETS, and the name Bupropion HBr XL tablets is used throughout the submission (request to DMETS for trade name was submitted on 12-JUL-2007). The Bupropion HBr XL tablets consist of a tablet core surrounded by a controlled release coating. The coating forms a membrane that is responsible for controlling the release of bupropion hydrobromide in vivo. Bupropion HBr XL Tablets, 174 mg, 348 mg, and 522 mg, have the same tablet core formulation (bupropion, b(4)

adjusted for tablet weight. The coating formulation consists of ethylcellulose, povidone that controls the release of bupropion hydrobromide for a prolonged period of time. The coating solution composition is qualitatively identical for two strengths, 174 mg and 348 mg, and differs from the 522 mg tablets by lacking the carnauba wax in the 522 mg tablets. b(4)

The manufacture of the additional drug product strength, 522 mg drug product consists of the same steps as that for the 174 mg and 348 mg strength, and the same analytical methods were utilized for release and stability resting of the 522 mg tablets.

The release specification for three dosage strengths of Bupropion HBr XL tablets include description, identification by HPLC and IR, uniformity of dosage form, drug release (dissolution), bupropion hydrobromide content, drug related impurities content, moisture content and residual solvents. After revision, the drug product specifications now include a second identification test , a specified moisture content limit of NMT and a reduced acceptance criterion . However, the specification limit for impurity is not justified, and Biovail should reduce the specification limit to that is accepted in the USP Monograph for Bupropion Hydrochloride Extended Release Tablets. Biovail did not adopt the dissolution specifications proposed by OCPB, and has proposed the interim dissolution specifications for all dosage strengths (174 mg, 348 mg and 522 mg) as follows: 2 hours – NMT dissolved, 4 hours dissolved, 8 hours –NLT dissolved (Amendment 10/23/2007, Complete Response to AE Letter). This interim dissolution specification is currently under review in the OCPB. Biovail commits to optimize the HPLC method for Assay and Impurities within six months from the date of NDA 22-108 approval. b(4)

The three batches of Bupropion HBr XL tablets of each strength, 174 mg, 348 mg and 522 mg were manufactured to-date at the commercial scale at the Biovail Corporation in Steinbach, Manitoba, Canada. The overall Acceptable recommendation from the Office of Compliance was received (June 07, 2007 and January 22, 2008) for drug substance and drug product manufacturing facilities of Bupropion HBr XL tablets (see Attachment 1 for detailed EES report). The batches of drug product tablets of two strengths, 174 mg and 348 mg, were manufactured using one lot of Bupropion HBr drug substance, and different drug substance lot was used for production of 522 mg strength. The release results of the drug substance batch 06PB0102 used to manufacture Bupropion tablets, 174 mg and 348 mg, are very similar to that of the drug substance batch 06PC0188 used to manufacture Bupropion tablets, 522 mg, and to that of the three batches of drug substance presented in . The comparison of the release data for batches of 522 mg tablets to that of the 174 mg and 348 mg shows the similarity of all these batches by the results of the tested parameters. The batch results of the 522 mg drug product demonstrated that all data was within the proposed specification b(4)

The applicant provided 12-month stability data at 25° C/60% RH and 6-month data at 40° C/75% RH for 3 batches of each 174 mg and 348 mg tablets, and 6-month stability data at 25° C/60% RH and at 40° C/75% RH for 3 batches of 522 mg tablets (all data provided for batches packaged in three different package configuration). The expiration b(4)

period for Bupropion HBr XL Tablets, 174 mg and 348 mg could be granted (as requested by Biovail) pending on the final adopted dissolution specifications. The expiration date could not be granted at this time for Bupropion HBr XL Tablets, 522 mg HBr XL Tablets. In order to assign the requested [redacted] expiry, Biovail should provide the 12-month stability data for this tablet strength. b(4)

DRUG SUBSTANCE

The sponsor references Type II DMF [redacted] for information on the drug substance Bupropion Hydrobromide [redacted] (LoA dated 12-MAY-05). [redacted] is reviewed and found inadequate (Review #2 by Dr. Lyudmila Soldatova, dated 18-JAN-2008). [redacted] has to address the deficiencies outlined in the IR Letter dated January 17, 2007. The drug substance is manufactured commercially by [redacted] [acceptable OC recommendation dated 07-JUN-2006]. Biovail has included a test and limit for particle size distribution, and set limits for bulk and tapped densities in the acceptance drug substance specifications. In addition, Biovail has reduced the specification limit [redacted] for the potential genotoxic impurity [redacted] in the drug substance specifications; described the HPLC analytical method for detection of this impurity with LOD of [redacted], and provided data that demonstrated the "Below LOD" level of this impurity in five Bupropion HBr batches. Biovail has to apply to USAN to obtain the established name for the hydrobromide salt of Bupropion. b(4)

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

The Bupropion hydrobromide extended release tablets, 174 mg, 348 mg, and 522 mg will be packaged as: [redacted] 30 ct in white bottles, 90 ct in white [redacted] bottles, [redacted]). b(4)

The recommended starting dose should be 174 mg/day as a single daily dose given in the morning. If the 174 mg dose is adequately tolerated, an increase to 522 mg/day, given once daily, can be made as early as day four.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F). (See USP Controlled Room Temperature).

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-108 for Bupropion Hydrobromide Extended Release Tablets is recommended **Approvable** from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Renmeet Grewal

C. CC Block

See DFS.

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/s/

Lyudmila Soldatova
2/29/2008 12:09:41 PM
CHEMIST

Ramesh Sood
2/29/2008 12:39:03 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**22-108**
Applicant:	Biovail Laboratories Intl.
Letter Date:	23-OCT-07
Stamp Date:	23-OCT-07
PDUFA Date:	To be determined
Trademark:	Not provided
Established Name:	Bupropion hydrobromide
Dosage Form:	174 mg, 348 mg, and 522 mg Extended-Release Tablets
Route of Administration:	Oral
Indication:	Major Depressive Disorder
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary
Bupropion hydrochloride is currently approved for use in an immediate release formulation (Wellbutrin® Tablets; AP 30-DEC-85), a sustained release formulation (Wellbutrin SR® Tablets; AP 04-OCT-96), and an extended release formulation (Wellbutrin XL® Tablets; AP 28-AUG-03). Bupropion hydrobromide extended release tablets were designed to be bioequivalent to the corresponding strengths of Wellbutrin XL® tablets (bupropion hydrochloride). The sponsor was sent a NA letter dated 19-JUL-07 (CMC and biopharm issues). In this submission, the applicant has responded to this NA letter. There were a total of 20 CMC issues detailed in the NA letter [one of which included notification that the DMF holder
was sent a deficiency letter]. The applicant has stated the responses to each of these issues were provided in previous submissions (dated 12-JUN-07, 28-JUN-07, and 03-JUL-07).

b(4)

Comments and Recommendation:
As Dr. Lyudmila Soldatova reviewed the original submission, she would be a prudent choice to review this response. The reviewer will need to determine whether the applicant has adequately responded to the CMC deficiencies. In addition, the new 522 mg strength will need to be reviewed; it was not reviewed in the first cycle as the amendment adding it was received quite late into the review cycle. Two sites were re-submitted into EES (01-NOV-07) for final update; the reviewer will need to verify no additional sites have been added by the applicant. The reviewer will also need to determine who will be evaluating dissolution.

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/s/

Thomas Oliver
11/1/2007 09:36:55 AM
CHEMIST

Ramesh Sood
11/1/2007 11:49:40 AM
CHEMIST

7/6/7

CHEMISTRY REVIEW

NDA 22-108

Bupropion Hydrobromide Extended-Release Tablets

Biovail Laboratories International SRL

DIVISION OF PSYCHIATRY DRUG PRODUCTS

Lyudmila N. Soldatova, Ph.D.
DPA I/ONDQA

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-108

2. REVIEW #1:

3. REVIEW DATE: June 22, 2007

4. REVIEWER: Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-SEP-2006
Amendment	13-NOV-2006
Amendment	22-DEC-2006
Amendment	24-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Biovail Laboratories International SRL Keller and Heckman, LLP (U.S. Agent)
Address:	Chelston Park, Building 2, Collymore Rock, St. Michael, BHI, Barbados, West Indies U.S. Agent's Address: 1001 G Street, N.W., Suite 500 West Washington, DC 20001
Representative:	John B. Dubeck (U.S. Agent)
Telephone:	202- 434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Bupropion Hydrobromide
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® Tablets, 150 mg and 300 mg, holder GlaxoSmithKlein.

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 174 mg and 348 mg

13. ROUTE OF ADMINISTRATION: Oral

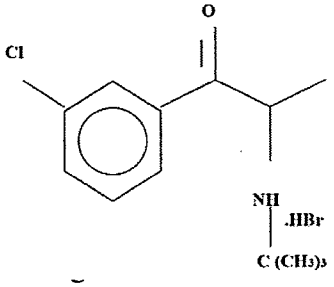
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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 Hydrobromide
Molecular Formula: $C_{13}H_{18}ClNO \cdot HBr$
Molecular Weight: 320.6 g/mole



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	05-16-2007	
	IV			4	N/A	Adequate information provided in review	b(4)
	III			3	Adequate	09-28-00 (reviewed by Dr. Klein)	
	III			3	Adequate	09-28-00 (reviewed by Dr. Klein)	
	III			3	Adequate	10-26-2001 (reviewed by Dr. J. Boal)	
	III			3, 4	Adequate	05-15-2007 (reviewed by Drs. W. Wilson and D. Klein). In addition, adequate information provided in review	
	III			1	Adequate	06-08-2007 (reviewed by Dr. L.Soldatova)	

[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 relevant 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
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
Clinical	No safety or other clinical concern; approvable/approval recommendation	28-JUN-2007	Robert Levin, MD
EES	Acceptable	07-JUN-2007	Office of Compliance
Pharm/Tox	Pending		Linda Fossom, Ph.D.
OCPB	Not acceptable	15-JUN-2007	Andre Jackson, Ph.D.
LNC	USAN is not available		
Methods Validation	Pending	Pending as per this review	Lyudmila N. Soldatova, Ph.D.
DMETS	Pending		
EA	Categorical Exclusion granted	As per this review	Lyudmila N. Soldatova, Ph.D.
Microbiology	N/A		

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The Chemistry Review for NDA 22-108

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-108 for Bupropion Hydrobromide Extended Release Tablets is recommended APPROVABLE from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance and drug product deficiencies, and on the adequate status of the DMF ———— b(4)

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)

BACKGROUND

Bupropion hydrochloride is currently approved for use in an immediate release formulation (Wellbutrin® Tablets; AP 30-DEC-85), a sustained release formulation (Wellbutrin SR® Tablets; AP 04-OCT-96), and an extended release formulation (Wellbutrin XL® Tablets; AP 28-AUG-03). Bupropion hydrobromide extended release tablets were designed to be bioequivalent to the corresponding strengths of Wellbutrin XL® tablets (bupropion hydrochloride).

DRUG PRODUCT

Bupropion hydrobromide extended release tablets will be available in two strengths: 174 mg and 348 mg for the treatment of major depressive disorder. The 348 mg/day dose is the targeted adult dose. The applicant has not selected a preferred trade name and hence the name Bupropion HBr XL tablets is used throughout the submission (request to DMETS for trade name ———— was submitted on 26-APR-2007). The Bupropion HBr XL tablets consist of a tablet core surrounded by a controlled release coating. The coating forms a membrane that is responsible for controlling the release of bupropion hydrobromide *in vivo*. Bupropion HBr XL Tablets, 174 mg and 348 mg, have the same tablet — formulation (bupropion ———— adjusted for tablet weight, ———— are directly proportional. The coating formulation consists of ———— , ethylcellulose, ———— povidone that controls the release of bupropion hydrobromide for a prolonged ————. The coating solution composition is qualitatively identical for both strengths, however, the quantitative amount of coating applied to each of the tablet b(4)

. The adequacy of the tablet coating and its effect on the batch to batch consistency was demonstrated by the comparable batch release results for three batches of each strength, 174 mg and 348 mg tablets, however, a noticeable difference was observed in the dissolution of two dosage strengths at 8 hours and 16 hours time points. The excipients used in the tablets formulation are common excipients of USP/NF compendial grade that are listed in the current FDA Inactive Ingredients Guide for approved drug products. The manufacture of the drug product consists of: . The applicant has adequately identified the critical steps , and provided the in-process controls and tests for these manufacturing steps. An unusually wide in-process control limits for Bupropion HBr XL uncoated Tablets were noticed that may have an impact on the dissolution of the Bupropion HBr XL Tablets. b(4)

The release specification include description, identification, uniformity of content, drug release (dissolution), bupropion hydrobromide content, drug related impurities content, moisture content and residual solvents. Biovail has proposed a higher limit for one of the known impurities, than that in the monograph for Bupropion HCl (NMT vs. NMT in the USP specifications for Bupropion HCl ER Tablets). This issue was communicated to the pharm/tox reviewer for evaluation/decision whether this limit is qualified in the appropriate toxicology studies. The other specification limits for the related known compounds are set tighter than that in the monograph for Bupropion HCl, however, they are above . Biovail should modify the description section of the specifications, to establish limit for water content, and to include a microbial limits parameter in the specification. The OCPB reviewer recommended different specification limits for dissolution than that proposed by Biovail. The applicant should address the OCPB recommendation. Validation of the analytical methods was provided; it is acceptable except for HPLC method for identification, assay and impurities. The applicant is requested to commit to optimize this HPLC method) in order to obtain a distinct separation of the diluent and impurity peaks. b(4)

The three batches of Bupropion HBr XL tablets of each strength, 174 mg and 348 mg were manufactured to-date at the commercial scale at the Biovail Corporation in Steinbach, Manitoba, Canada. All batches of drug product tablets of both strengths, 174 mg and 348 mg, were manufactured using one lot of Bupropion HBr drug substance. The overall Acceptable recommendation from the Office of Compliance was received (June 07, 2007) for drug substance and drug product manufacturing facilities of Bupropion HBr XL tablets. The batch results demonstrated that all data for individual tablet strengths was within the proposed specification. The data for batches within the strengths demonstrated good batch-to-batch consistency for all attributes except for weight variation, though the data was within the %RSD $\leq$ 6%.

The applicant provided 6-months stability data at 25° C/60% RH and at 40° C/75% RH for 3 batches of each strength, packaged in three different package configuration, and stability data for the same three batches stored at bulk warehouse conditions. The expiration date could not be granted at this time for Bupropion HBr XL Tablets, 174 and 348 mg since at

least 12 months of stability data is required for this purpose. In addition, it should be noticed that only one lot of Bupropion HBr drug substance manufactured ——— was used to manufacture all Bupropion HBr XL Tablets of both strengths, 174 mg and 348 mg. According to ICH Guidance Q1A(R2), different batches of the drug substance should be used in the manufacture of the primary stability batches of the drug product. b(4)

On April 26, 2007, Biovail submitted Amendment to the original submission that provides for an additional strength of a 522 mg bupropion hydrobromide extended-release tablet. After discussion of this submission with ONDQA team (Dr. Thomas Oliver, Dr. Ramesh Sood and Dr. Blair Fraser) and with the Division of Psychiatry Drug Products (Dr. Thomas Laughren), it was decided that this submission should not be reviewed due to the late timeframe in the PDUFA review clock. The applicant should use alternative possibilities to submit this additional information. b(4)

DRUG SUBSTANCE

The sponsor references ——— for information on the drug substance Bupropion Hydrobromide ——— (LoA dated 12-MAY-05). Bupropion hydrobromide is a member of the aminoketone class of compound; it is a white to almost white crystalline powder that is soluble in water. Bupropion hydrobromide contains a chiral center, but the compound has been developed as a racemate. The drug substance is manufactured commercially ——— ——— [overall acceptable OC recommendation dated 07-JUN-2006]. ——— is reviewed and found inadequate (Review #1 by Dr. Lyudmila Soldatova, dated 16-MAY-2007). The separate subsections of the drug substance Bupropion Hydrobromide are summarized ——— in NDA submission. In addition, Biovail proposed the in-house acceptance drug substance specifications, HPLC method for identification, assay and impurities, and GC method for residual solvents. Biovail should include a test and limit for particle size distribution in the acceptance drug substance specifications. In addition, Biovail should address the issue on the level of potential genotoxic impurity, ——— ——— in the drug substance batches (pharm/tox reviewer was alerted on this issue). b(4)

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

The Bupropion hydrobromide extended release tablets, 174 and 348 mg, will be packaged as: ——— 30 ct in white ——— bottles, and 90 ct in white ——— bottles ——— ——— b(4)

The recommended starting dose should be 174 mg/day as a single daily dose given in the morning. If the 174 mg dose is adequately tolerated, an increase to 348 mg/day, given once daily, can be made as early as day four. The 348 mg/day dose is the targeted adult dose.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F). (See USP Controlled Room Temperature).

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-108 for Bupropion Hydrobromide Extended Release Tablets is recommended **Approvable** from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Renmeet Grewal

C. CC Block

See DFS.

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/s/

Lyudmila Soldatova
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CHEMIST

Ramesh Sood
7/6/2007 07:52:04 AM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**22-108**
Applicant:	Biovail Laboratories Intl.
Letter Date:	27-SEP-06
Stamp Date:	28-SEP-06
PDUFA Date:	28-JUL-07
Trademark:	Not provided
Established Name:	Bupropion hydrobromide
Dosage Form:	174 mg and 348 mg Extended-Release Tablets
Route of Administration:	Oral
Indication:	Major Depressive Disorder
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary
Bupropion hydrochloride is currently approved for use in an immediate release formulation (Wellbutrin® Tablets; AP 30-DEC-85), a sustained release formulation (Wellbutrin SR® Tablets; AP 04-OCT-96), and an extended release formulation (Wellbutrin XL® Tablets; AP 28-AUG-03). Bupropion hydrobromide extended release tablets were designed to be bioequivalent to the corresponding strengths of Wellbutrin XL® tablets (bupropion hydrochloride). There appears to have been no EOP2 or pre-NDA meetings with the NDA holder on bupropion hydrobromide extended release tablets.

Drug Substance
The sponsor references _____ for information on the drug substance (LoA dated 12-MAY-05). Bupropion hydrobromide is a white to almost white crystalline powder that is soluble in water. Bupropion hydrobromide contains a chiral center, but the compound has been developed as a racemate. The drug substance will be manufactured commercially _____ will need to be reviewed. b(4)

Drug Product
Bupropion hydrobromide extended release tablets will be available in two strengths: 174 mg and 348 mg for the treatment of major depressive disorder. The recommended starting dose should be 174 mg/day as a single daily dose given in the morning. If the 174 mg dose is adequately tolerated, an increase to 348 mg/day, given once daily, can be made as early as day four. The 348 mg/day dose is the targeted adult dose. The bupropion HBr XL tablets consist of a tablet core surrounded by a controlled release coating. The sponsor uses common excipients of USP compendial grade. The 174 mg and 348 mg uncoated tablet cores are directly proportional (bupropion, _____ however, the final coated tablets are not. The components of the coating solutions used for both strengths are identical, but the composition of the coating b(4)

solutions is different. The coating formulation consists of ethylcellulose, povidone that controls the release of bupropion hydrobromide for a prolonged period of time. b(4)

The sponsor lists Biovail Corporation in Steinbach, Manitoba, Canada as the manufacturer of bupropion hydrobromide extended release tablets. The bupropion hydrobromide extended release tablets will be packaged as: 30 ct in white bottles, and 90 ct in white bottles.

Critical Issues for Review

- The sponsor has set drug substance specification limits of NMT b(4)

These specification limits will need to be discussed with pharm/tox and found acceptable (especially if a concern arises over any carcinogenicity or mutagenicity potential associated with any of these impurities).

- The role of particle size on product performance will need to be evaluated, to ensure adequate controls are in place for consistent product performance. The sponsor will need to demonstrate that particle size as measured in clinical, stability and commercial batches is rationally controlled to ensure product performance (as outlined in labeling).

- The sponsor's states the drug substance exists in a single unique crystalline form, however, the information to support this claim will need to be evaluated.

- The compatibility of the excipients used in the drug product will need to be evaluated.

-The sponsor cites two excipients (ethylcellulose and povidone) that control the release of bupropion hydrobromide. The sponsors understanding and control of each of these excipients will need to be closely examined. In addition, the adequacy of the tablet coating and the respective controls in place for batch to batch consistency will be critical.

- The sponsor incorporates a overage of polyvinyl alcohol/ . The sponsor's use of this overage will need to be evaluated in conjunction with the testing results. b(4)

- The 174 and 348 mg tablets are white to off-white round tablets. The sponsor has chosen four time points (2h, 4h, 8h, and 16h) for dissolution measurement. The adequacy of the dissolution specification will need to be evaluated in conjunction with the Biopharm reviewer. The dissolution specification (test, method, limit) and test results will need to be evaluated: 1) during IND development, 2) bioequivalence/ clinical

studies, and 3) stability. Any differences (including between strengths) will need to delineated and evaluated.

• The sponsor has set the specification limits higher for a number of drug product impurities than the recommended ICH Q3B limits. These limits will need to be evaluated in conjunction with the pharm/tox reviewer.

• The photostability study will need to be evaluated and the labeling will need to reflect any observations.

• It appears the dose strengths are expressed as bupropion hydrobromide (i.e., a 174 mg tablet contains 174 mg of bupropion hydrobromide). The 174 mg bottle labels lists bupropion hydrobromide and 174 mg, however, the reviewer will need to evaluate this issue.

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. The sponsor has claimed a categorical exclusion [25.31(a)] to the environmental analysis. Two sites were submitted into EES (11-OCT-06), however, the reviewer will need to confirm with the NDA holder that these are the only two sites, as this information was not depicted very clearly.

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/s/

Thomas Oliver
10/16/2006 09:22:26 AM
CHEMIST

Ramesh Sood
10/16/2006 09:28:28 AM
CHEMIST