

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75491

BIOEQUIVALENCY REVIEW(S)

8

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 75-491

SPONSOR: Mylan Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM: **Bupropion Hydrochloride Tablets**

STRENGTH (S): **75 mg and 100 mg**

TYPES OF STUDIES: Fasted Bioequivalence Study and Dissolution Testing

CLINICAL STUDY SITE (S)

ANALYTICAL SITE (S): Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

STUDY SUMMARY: Fasted ~~and Fast~~ Bioequivalence Studies are acceptable

DISSOLUTION: Dissolution testing is acceptable.

DSI INSPECTION STATUS

Inspection needed:

NO

Inspection status:

Inspection results:

First Generic No

Inspection requested: (date)

New facility

Inspection completed: (date)

For cause

Other

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D.

BRANCH : I

INITIAL : CS

DATE : 3/9/00

TEAM LEADER : YIH-CHAIN HUANG, Ph. D.

BRANCH : I

INITIAL : YH

DATE : 3/10/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DC

DATE : 3/17/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 75-491

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Tablets, 75mg and 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

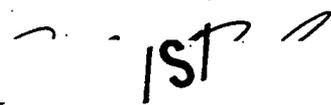
The following dissolution testing should be incorporated into your stability and quality control programs:

The dissolution should be conducted in 900 mL of water at 37 °C using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,


Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Bupropion HCl Tablets
75 and 100 mg
ANDA #75-491
Reviewer: Chandra S. Chaurasia

Mylan Pharmaceuticals, Inc.
Morgantown, WV 26504
Submission date:
February 18, 2000

Review of an Amendment

I. Objective

Review of Mylan's amendment responding to the deficiency letter by the Division of Bioequivalence dated February 18, 2000.

II. Background

Mylan previously submitted a single dose in vivo bioequivalence study under fasting conditions comparing its 100-mg bupropion hydrochloride tablets, lot #2E002B, to Wellbutrin® 100-mg tablet, manufactured by Glaxo Wellcome (Submission Date: October 30, 1998; Review Date: January 31, 1999). The biostudy was found incomplete due to the absence of reports on long-term frozen stability.

In the ANDA submission dated October 30, 1998, the firm had reported only a seven-day long-term study at -70 °C for bupropion and its metabolites hydroxybupropion and threohydrobupropion. It is to be noted that the biostudy was conducted from 03/27/98 to 04/26/98, and the sample analyses were done from 07/27/98 to 09/04/98. Thus, the samples were stored at -70 °C for a period of 161 days.

In the ANDA submission dated October 30, 1998, Mylan had also submitted dissolution data comparing its 100-mg bupropion hydrochloride tablets, lot #2E002B, to Wellbutrin® 100-mg tablets. The dissolution testing was found acceptable. In addition, the firm had also submitted dissolution testing results for its 75-mg bupropion hydrochloride tablets as part of a waiver request on this strength. The sponsor's 75-mg bupropion hydrochloride tablets were deemed bioequivalent to the 75-mg Wellbutrin® tablets pending long-term frozen stability study on the sponsor's bupropion hydrochloride 100-mg tablets.

III. Review of the Firm's Response

Deficiency: You have submitted frozen stability data for 7-day period only. In the absence of reports on long-term frozen

study, the analytical assay validation and hence the biostudy is incomplete.

Response:

The firm has provided additional long term frozen stability data for bupropion, hydroxybupropion and threohydrobupropion in plasma stored at -70 °C for 175 days (Vol. 2.1, pp. 8-12). The samples were initially analyzed (before freezing) with a standard curve and their initial concentrations were determined. The samples were again analyzed after 175 days at -70 °C along with a standard curve and fresh controls. The mean calculated concentrations were within $\pm 15\%$ of the theoretical concentrations.

IV. Comments

The long-term frozen stability data and the assay validation for quantitation of bupropion, and its metabolites hydroxybupropion and threohydrobupropion in human plasma are acceptable.

V. Recommendations

1. The single-dose bioequivalence study under fasting conditions, conducted by Mylan Pharmaceuticals, Inc., on its Bupropion Hydrochloride, 100-mg tablets, Lot #2E002B, comparing it to Wellbutrin® 100-mg tablet, manufactured by Glaxo Wellcome has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Bupropion Hydrochloride 100-mg tablets are bioequivalent to the reference product Wellbutrin®, 100-mg tablets manufactured by Glaxo Wellcome.
2. The dissolution testing conducted by Mylan Pharmaceuticals, Inc. on its Bupropion Hydrochloride, 100-mg tablets, Lot #2E002B, and is acceptable.
3. The dissolution testing conducted by Mylan Pharmaceuticals, Inc. on its Bupropion Hydrochloride, 75-mg tablets, Lot 2E001B is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing its 100-mg tablets of the test product with 100-mg tablets of the reference product Wellbutrin® manufactured by Glaxo Wellcome. The formulation for the 75-mg strength is proportionally similar to the 100-mg strength of the test product, which underwent bioequivalence testing. The 75-mg Bupropion

Hydrochloride tablet of the test product is therefore deemed bioequivalent to the 75-mg tablet Wellbutrin® manufactured by Glaxo Wellcome.

4. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should be conducted in 900 mL of water at 37 °C using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

ISI
Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 3/9/00

RD INITIALED YHUANG
FT INITIALED YHUANG

ISI 3/10/2000

Concur: ISI
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

3/17/00

ANDA:75-491; Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Tablets, 75mg and 100 mg

1.1
[copy]

BIOEQUIVALENCY DEFICIENCIES

ANDA:75-491.

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion HCl Tablets 75 and 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You have submitted frozen stability data for a 7-day period only. In the absence of reports on long-term frozen study, the analytical assay validation and hence the biostudy is incomplete.

Sincerely yours,

JSP
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-491
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)

HFD-652/CS Chaurasia *UC*
HFD-652/YC Huang *YH 1/26/99*
HFD-617/Elaine Hu
HFD-650/Dale Conner *DA 1/31/99*

Insert Path and File Name Here

Printed in Final on 01/26/99

BIOEQUIVALENCY - DEFICIENCIES

Submission Date:10/30/98

1. **FASTING STUDY (STF)**

Clinical:
Analytical: As above

Strengths: 100mg

Outcome: IC

2. **DISSOLUTION WAIVER (DIW)**

Strengths: 75mg

Outcome: IC

Outcome Decisions:

AC - Acceptable

UN - Unacceptable

NC - No Action

IC - Incomplete

WinBio Comments:

- Fasting study of 100 mg tablet is incomplete
- Request for in vivo biowaiver on 75 mg tablet is incomplete

Table 1A

Mean Plasma Bupropion levels (ng/mL) and the derived pharmacokinetic measures following an oral dose of 1x100 mg, bupropion HCl tablet, fasted conditions, n=39

Time (hr)	Test Product*	Reference Product*	Test/Reference
0.0	0.0	0.0	-
0.25	0.83 (244.9.5)	0.36 (272.2)	2.3
0.50	46.42 (102.5)	8.17 (127.8)	5.7
0.75	112.27 (53.2)	78.04 (74.7)	1.4
1.0	120.52 (34.2)	109.61 (46.3)	1.1
1.50	105.57 (33.0)	113.13 (32.8)	0.9
2.00	86.90 (36.2)	91.75 (32.7)	0.9
3.00	58.82 (36.5)	63.31 (32.9)	0.9
4.00	41.35 (29.1)	44.73 (34.1)	0.9
6.00	23.80 (36.6)	23.71 (33.3)	1.0
8.00	16.14 (37.8)	15.44 (33.2)	1.0
12.00	9.00 (34.0)	8.57 (29.9)	1.1
18.00	4.85 (38.8)	4.76 (37.7)	1.1
24.00	3.30 (48.1)	3.20 (46.5)	1.0
36.00	1.26 (107.5)	1.11 (129.5)	1.1
48.00	0.20 (355.7)	0.23 (300.9)	0.9
72.00	0	0.17 (634.5)	-
96.00	0	0.25 (616.4)	-
144.00	0	-	-
192.00	0	-	-

*Data are arithmetic mean values (%CV)

PK Measures	Test	Reference	T/R	90% CI [§]
AUC _t (ng*hr/mL)**	525.5±180.1	518.1±156.7		
AUC _i (ng*hr/mL)**	568.0±196.7	568.4±178.6		
C _{max} (ng/mL)**	136.3±51.8	136.2±45.1		
Ln AUC _t	6.20180059	6.20007718		95-106%
Geometric mean	493.6	492.8	1.00	
Ln AUC _i	6.28767734	6.28613279		95-106%
Geometric mean	537.9	537.1	1.00	
Ln C _{max}	4.84154298	4.85414997		90-109%
Geometric mean	126.7	128.3	0.99	

**Data are arithmetic mean values (±S.D)

[§]Used Natural Log Transformed Parameter

Table 1B

Mean Plasma Hydroxy bupropion levels (ng/mL) and the derived pharmacokinetic measures following an oral dose of 1x100 mg, bupropion HCl tablet, fasted conditions, n=39

<u>Time (hr)</u>	<u>Test Product*</u>	<u>Reference Product*</u>	<u>Test/Reference</u>
0.0	0.0	0.0	-
0.25	3.17 (166.5)	1.19 (239.5)	2.7
0.50	62.42 (74.6)	21.49 (93.6)	2.9
0.75	137.41 (42.8)	96.20 (63.1)	1.4
1.0	182.35 (35.6)	152.52 (46.1)	1.2
1.50	220.49 (33.9)	220.18 (36.2)	1.0
2.00	238.43 (33.7)	237.41 (32.2)	1.0
3.00	254.07 (34.8)	258.18 (31.1)	1.0
4.00	253.86 (33.3)	254.40 (28.7)	1.0
6.00	241.89 (33.5)	239.18 (30.0)	1.0
8.00	229.24 (29.9)	224.82 (28.1)	1.0
12.00	198.23 (29.7)	196.29 (28.7)	1.0
18.00	160.64 (33.8)	158.16 (32.5)	1.0
24.00	148.02 (38.6)	146.05 (30.2)	1.0
36.00	96.56 (39.8)	95.85 (31.5)	1.0
48.00	68.91 (47.3)	67.00 (39.5)	1.0
72.00	30.92 (61.3)	28.81 (49.5)	1.1
96.00	13.58 (77.4)	12.59 (62.4)	1.1
144.00	0.93 (380.2)	0.94 (244.0)	1.0
192.00	0.87 (391.2)	0.23 (600.0)	3.4

*Data are arithmetic mean values (%CV)

PK Measures	Test	Reference	T/R	90% CI [§]
AUC _t (ng*hr/mL)**	8915.0±3325.2	8708.4±2792.0		
AUC _i (ng*hr/mL)**	9453.8±3447.5	9111±2824.6		
C _{max} (ng/mL)**	269.0±87.8	269.8±79.2		
Ln AUC _t	9.03748278	9.02301591		97-106%
Geometric mean	8412.6	8291.7	1.01	
Ln AUC _i	9.09025737	9.07077420		98-106%
Geometric mean	8868.5	8697.4	1.02	
Ln C _{max}	5.54561434	5.55557625		95-104%
Geometric mean	256.1	258.7	0.99	

**Data are arithmetic mean values (±S.D)

[§]Used Natural Log Transformed Parameter

Table 1C

Mean Plasma Threohydroxy bupropion levels (ng/mL) and the derived pharmacokinetic measures following an oral dose of 1x100 mg, bupropion HCl tablet, fasted conditions, n=39

Time (hr)	Test Product*	Reference Product*	Test/Reference
0.0	0.0	0.0	-
0.25	0.0	0.0	-
0.50	6.54 (9.4)	0.48 (2.3)	13.6
0.75	36.46 (27.4)	19.66 (20.8)	1.9
1.0	59.74 (27.1)	46.08 (31.3)	1.3
1.50	74.31 (24.9)	73.88 (31.1)	1.0
2.00	77.20 (23.8)	75.04 (25.8)	1.0
3.00	68.82 (19.6)	73.19 (22.5)	0.9
4.00	65.10 (20.6)	67.25 (22.9)	1.0
6.00	57.85 (18.3)	57.47 (17.4)	1.0
8.00	52.62 (15.9)	51.54 (16.9)	1.0
12.00	42.76 (12.9)	42.13 (12.7)	1.0
18.00	34.41 (11.4)	34.51 (13.0)	1.0
24.00	29.47 (10.4)	29.59 (9.2)	1.0
36.00	24.81 (7.6)	25.02 (8.0)	1.0
48.00	20.17 (6.4)	20.61 (5.8)	1.0
72.00	13.71 (4.6)	13.70 (4.4)	1.0
96.00	8.92 (4.5)	8.44 (4.7)	1.1
144.00	2.58 (3.6)	2.42 (3.6)	1.1
192.00	0.32 (1.3)	0.59 (2.1)	0.5

*Data are arithmetic mean values (%CV)

PK Measures	Test	Reference	T/R	90% CI [§]
AUC _t (ng*hr/mL)**	2526.7±772.0	2506.0±724.4		
AUC _i (ng*hr/mL)**	3056.6±831.7	3005.0±857.9		
C _{max} (ng/mL)**	85.9±24.2	88.8±28.0		
Ln AUC _t	7.78364819	7.78629691		
Geometric mean	2401.0	2407.4	1.00	94-106%
Ln AUC _i	7.98256689	7.97766942		
Geometric mean	2929.4	2915.1	1.00	95-107%
Ln C _{max}	4.41109817	4.43825193		
Geometric mean	82.4	84.6	0.97	91-104%

**Data are arithmetic mean values (±S.D)

§Used Natural Log Transformed Parameter

Table 2. In vitro dissolution testing

Drug name: Bupropion Hydrochloride Tablets
 Dose strength: 75 and 100 mg
 ANDA No. 75-491
 Firm: Mylan, Pharmaceuticals, Inc.
 Submission date: 10/30/98

Conditions of dissolution testing

Method: USP 23 Apparatus 2 (paddle) 50 rpm, water, 900 mL at 37±0.5°C
 Proposed Specifications: NTL % (Q) dissolved in 45 minutes
 RLD: Wellbutrin® tablets
 Assay methodology:

Results of dissolution testing for 100 mg bupropion HCl tablets

Sampling time (min)	Test product Lot No. #2E002B Strength 100 mg			Reference product Lot No. 7F2349 Strength 100 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	91%		5.6%	85%		10.9%
30	95%		3.4	93%		6.5%
45	96%		2.6	97%		4.2%

Results of dissolution testing for 75 mg bupropion HCl tablets

Sampling time (min)	Test product Lot No. #2E001B Strength 75 mg			Reference product Lot No. 7H1579 Strength 75 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	99%		1.9%	88%		7.3%
30	100%		1.3%	98%		4.1%
45	101%		1.0%	101%		3.0%

Fig . 1A. Mean Bupropion Plasma Concentrations-Time Plot, 1x100 mg tablef, n=39

Time (hr)	TEST	REF
0.00	0	0
0.25	0.83	0.36
0.50	46.42	8.17
0.75	112.27	78.04
1.00	120.52	109.61
1.50	105.57	113.13
2.00	86.9	91.75
3.00	58.82	63.31
4.00	41.35	44.73
6.00	23.8	23.71
8.00	16.14	15.44
12.00	9	8.57
18.00	4.85	4.76
24.00	3.3	3.2
36.00	1.26	1.11
48.00	0.2	0.23
72.00	0	0.17
96.00	0	0.25
144.00	0	0
192.00	0	0

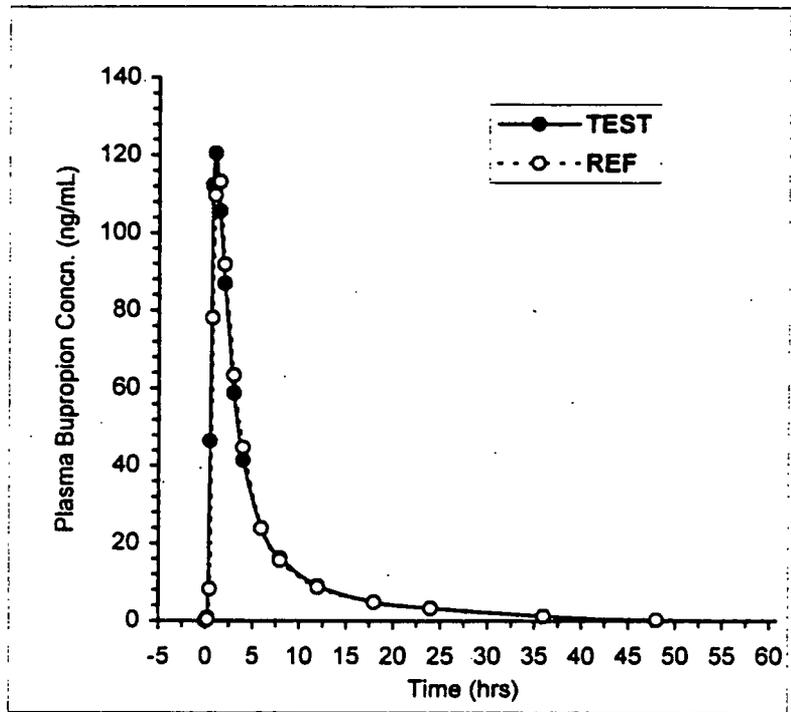


Fig 1B. Mean Hydroxybupropion Plasma Concentrations-Time Plot, 1x100mg tablet, n=39

	TEST	REF
0.00	0.0	0.0
0.25	3.2	1.2
0.50	62.4	21.5
0.75	137.4	96.2
1.00	182.4	152.5
1.50	220.4	220.2
2.00	238.4	237.4
3.00	254.1	258.2
4.00	253.9	254.4
6.00	241.9	239.2
8.00	229.2	224.8
12.00	198.2	196.3
18.00	160.6	158.2
24.00	148.0	146.1
36.00	96.6	95.9
48.00	68.9	67.0
72.00	30.9	28.8
96.00	13.6	12.6
144.00	0.9	0.9
192	0.9	0.2

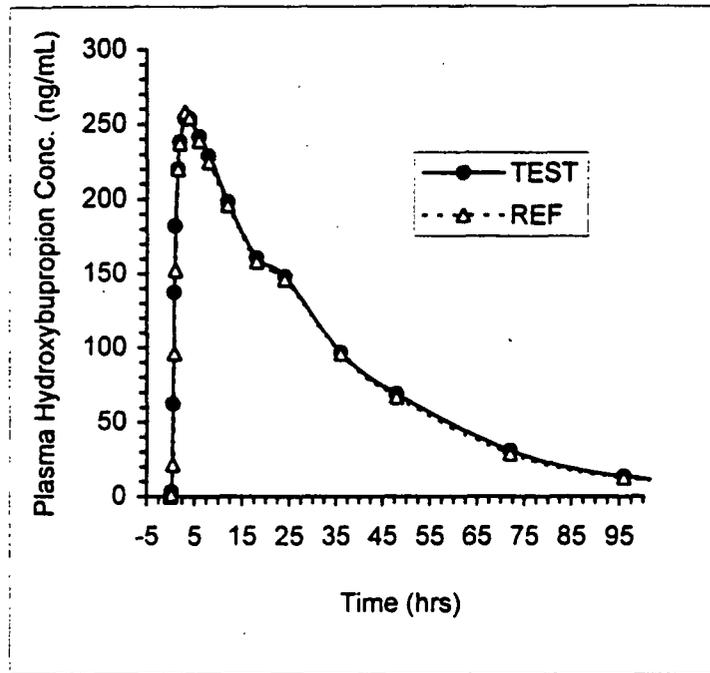
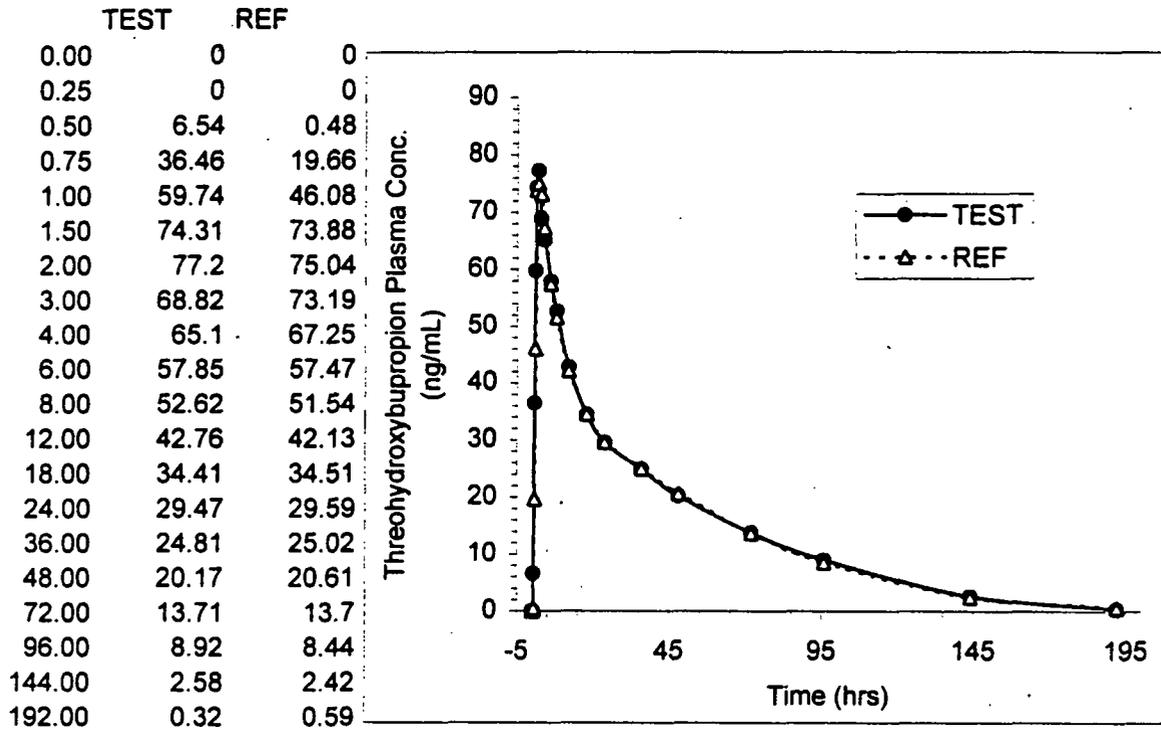


Fig. 1C. Mean Plasma Threohydroxybupropion Concentration-Time Plot, 1x100 mg tablet, n=39



Bupropion HCl Tablets
75 and 100 mg
ANDA #75-491
Reviewer: Chandra S. Chaurasia

Mylan Pharmaceuticals, Inc.
Morgantown, WV 26504
Submission date:
October 30, 1998

Review of a Bioequivalence Study and Dissolution Data

I. Introduction

Indication: Treatment of Depression

Type of Submission: Original ANDA

Contents of Submission: Fasting bioequivalence study and
Dissolution data

RLD: Wellbutrin® 75 and 100 mg (manufactured by Glaxo Wellcome)

II. Background

Bupropion Hydrochloride tablet is an immediate release product for bupropion. Bupropion is an antidepressant of the aminoketone class.

Following oral administration of bupropion, peak plasma bupropion concentrations are usually achieved within 2 hours, followed by a biphasic decline. The average half-life of the post-distributional phase is approximately 14 hours, with a range of 8 to 24 hours. Six hours after a single dose, plasma bupropion concentrations are approximately 30% of peak concentrations.

Several of the known metabolites of bupropion are pharmacologically active, but their potency and toxicity relative to bupropion have not been fully characterized. Four basic metabolites of bupropion have been identified. They are the erythro- and threo-amino alcohols of bupropion, the erythro-amino diol of bupropion, and a morpholinol metabolite. The erythro-amino alcohol and erythro-amino diol metabolites generally can not be detected in the systemic circulation following a single oral dose of the parent drug. The morpholinol metabolite appears in the systemic circulation almost as rapidly as the parent drug following a single oral dose. Its peak level is three times the peak level of the parent drug.; it has a half-life in the order of 24 hours, and its AUC₀₋₆₀ is about 15 times that of bupropion.

In the agency letter of Dec. 5, 1997 to Mylan Pharmaceuticals, Inc. (see attached), it was recommended that for single-dose studies of immediate-release bupropion hydrochloride tablets, concentrations of bupropion, threo-amino alcohol and the morpholinol metabolite should be measured; and the concentrations of erythro-amino alcohol metabolite may also be measured by an achiral assay with the threo-amino alcohol metabolite.

III. Protocol No. BUPR-9764: A Two-Way Crossover Single-Dose, Randomized Study to Determine the Bioequivalence of Two Oral Bupropion Formulations (1x 100 mg tablets)

A. Study Information

Clinical Site:

Investigators:

Subjects: Entered - 41 normal healthy subjects (all males)
Completed - 39

Inclusion Criteria: Listed in Vol. 1.5, page 1666. Subjects who participated in the study were in the age range of 18-45 years, and within 10% of their ideal body weight as specified in the protocol.

Restrictions: Listed in Vol. 1.5, page 1667. The protocol also specified that subjects were not to take any medication including OTC products, for 14 days prior to the initial dose of medication, during the study, or during the washout period. Subjects abstained from xanthine- or caffeine-containing foods or beverages within 48 hours prior to the initial dosing and during the study.

Study Dates: n=39, Period 1: 03/27/98 to 04/05/98
n=39, Period 2: 04/17/98 to 04/26/98

Randomization: A = reference, B = test
A,B: 1,3,5,8,11,12,13,14,19,20,21,
23,25,26,30,31,33,34,37,39,41

B,A: 2,4,6,7,9,10,15,16,17,18,22,
24,27,28,29,32,35,36,38,40

Study Design: Single-dose Fasting, two-way crossover

Washout Period: 21 days

Confinement: From 9:00 PM on the evening prior to dosing and until after the 24 hr blood draw.

Dosing: Subjects fasted overnight from 10 hours prior to until 5 hours post-dosing. Each oral dose (1x100 mg) was administered with 240 mL of water.

Analytical Site: Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

Analytical Director: Michael Adams

Analysis Dates: 07/27/98 through 09/04/98

Storage Period: not more than 160 days at -70 °C

Test Product: Bupropion HCl tablets (100 mg)
Mylan Pharmaceuticals, Inc.
Lot #2E002B
Manufacturing Date 2/06/98
Expiration Date N/A
Potency 98%, Content Uniformity 99.3% (RSD 1.8%)
Batch Size : tablets

Reference Product: Wellbutrin® tablets (100mg)
Glaxo Wellcome
Lot #7F2349, Expiration Date 07-99
Potency 98.1%, Content Uniformity 101.0% (RSD 1.1%)
Commercial Lot

Blood Sampling: Seven mL each, prior to dosing (time 0) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12, 18, 24, 36, 72, 96, 144 and 192 hours post-dose. Plasma samples were extracted and stored at -70 °C ±15 until analysis.

B. Study Results

1. Clinical (39 subjects completed the study)

Dropouts: Subject #20 was discontinued from study in period 2 due to intoxication. Subject #22 was discontinued from the study in Period 2 prior to dosing due to an asymptomatic adverse experience that was not study related. The reviewer concurs with this decision.

Adverse events: One (1) adverse event was reported during the study. This was possibly or probably not drug related. Subject #22 exhibited an asymptomatic experience (multiple PVC's noted on predose ECG) before dosing in Period 2 (Volume 1.2, 323 and Attachment 4, Table T-3, Volume 1.5, page 1659).

Protocol Deviations: None other than minor sampling deviations.

2. Analytical

Method:

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confidential

commercial

information

Analytical methods

3. Pharmacokinetic/Statistical Analysis

Pharmacokinetic Measures: Tables 1A-C and Figures 1A-C

90% Confidence Intervals: Tables 1A-C

Comments:

1. The pharmacokinetic measures (AUC_t , AUC_i and C_{max}) and 90% confidence intervals for bupropion, its hydroxy- and threohydroxy-metabolites, re-calculated by the reviewer were in good agreement with the values determined by the firm.
2. There were no statistically significant period or sequence effects for any of these PK measures.
3. The 90% confidence intervals for ln-transformed AUC_t , AUC_i , and C_{max} ratios are within the acceptable limits of 80-125%.

IV. Deficiency: The firm has submitted frozen stability data only for 7 days. In the absence of reports on long-term frozen study, the analytical assay validation and hence the biostudy is incomplete. The firm should be informed of this deficiency.

V. Formulation: The test formulation for bupropion hydrochloride tablets, 100 mg, is given below.

Quantitative Composition, Bupropion Hydrochloride Tablets, - 100 mg		
Ingredient	% (w/w)	mg/tablet
bupropion✓		
✓Colloidal Silicon Dioxide,		
✓Stearic acid, NF		
✓Anhydrous Lactose		
✓Microcrystalline Cellulose,		
✓Crospovidone, NF		
TOTAL THEORETICAL CORE WEIGHT		
✓Blue Solids		
Solids contribution from Blue		
Clear Aqueous Film-coating Solution (Clear		
Solids contribution from Clear		
Total	100	620

* Removed during manufacturing process
 Production batch size = tablets

VI. Waiver Request for 75 mg Strength and Dissolution Study

1. The firm has used the FDA recommended method with the following specifications:

- USP Paddle Method (Apparatus 2), 50 RPM
- Medium: 900 mL of simulated intestinal fluid w/o enzyme at 37 °C
- Tolerance: NLT (Q) $\frac{1}{2}$ in 45 minutes.

Date of Assay: 02/25/98

Number of tablets: 12

Test product:

Mylan Bupropion Hydrochloride 100 mg, Lot No. #2E002B

Mylan Bupropion Hydrochloride 75 mg, Lot No. #2E001B

Reference product:

Wellbutrin 100 mg, Lot #7F2349; Exp. Date: Jul. 1999

Wellbutrin 75 mg, Lot #7H1579; Exp. Date: Oct. 1999

Results: See Table 2.

Comments:

1. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies.
2. The dissolution method is acceptable.

Comparative Quantitative Compositions of Bupropion Hydrochloride 75 and 100 mg Tablets are given in the table below:

Strength per tablet	75mg		100 mg	
	%(w/w)	mg/tab	%(w/w)	mg/tab
ACTIVE INGREDIENT				
Bupropion		75.0		100.0
INACTIVE COMPONENTS				
Colloidal Silicon Dioxide, NF				
Stearic acid, NF				
Anhydrous Lactose NF				
Microcrystalline Cellulose,				
Crospovidone, NF				
Orange Solids				
Blue				
Clear				
TOTAL THEORETICAL WEIGHT	100%	465.0	100%	620.0

BIOEQUIVALENCY DEFICIENCIES

ANDA:75-491.

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Bupropion HCl Tablets 75 and 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

You have submitted frozen stability data for a 7-day period only. In the absence of reports on long-term frozen study, the analytical assay validation and hence the biostudy is incomplete.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research